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CONTENTS OF VOLUME 42

JULY, 1928 NUMBER 1

	PAGE
Thyroid Disease An Experimental Study Warren B Cooksey, M D, and M S Rosenblatt, M D, Detroit	1
Cardiazol' Some Experimental Effects of This Drug on the Cardiorespiratory Mechanism M Herbert Barker, M D, and Samuel A Levine, M D, Boston	14
The Electrocardiogram in Diphtheria M H Nathanson, M D, Minneapolis	23
Basal Metabolism III Influence of Work, with Special Reference to the Thyroid Gland James H Smith, M D, Richmond, Va	47
Tolerance for Quinine in Exophthalmic Goiter Israel Bram, M D, Philadelphia	53
Experimental Hypotension in Rabbits Theodore L Squier, M D, and Catherine T Bach, Milwaukee	56
The Utilization of Jerusalem Artichokes by a Patient with Diabetes Thorne M Carpenter, Ph D, and Howard F Root, M D, Boston	64
Disease of the Coronary Arteries Its Occurrence Without Gross Cardiac Hypertrophy H R Miller, M D, New York, and Morris M Weiss, M D, Louisville, Ky	74
Alkalosis in Patients with Peptic Ulcer Wesley E Gatewood, M D, Portland, Ore, Oliver H Gaebler, Ph D, New York, and Edward Muntwyler, Ph D, and Victor C Myers, Ph D, Cleveland	79
Total Chloride Concentration and Acidity of the Gastric Contents A Comparative Study F D Gorham, M D, C Malone Stroud, M D, and Maitland Huffman, M D, St Louis	106
Gastric Secretion Its Alteration by the Use of Atropine, Epinephrine and Pilocarpine A M Altshuler, M D, Detroit	117
Area of the Body Surface and Measurements of the Normal Heart A Preliminary Report R W Kissane, M D, Columbus, Ohio	135
Book Reviews	148

AUGUST, 1928 NUMBER 2

Epidemic Encephalitis as Observed at the First Czech Medical Clinic in Prague L Syllaba, M D, and K Henner, M D, Prague, Czechoslovakia	151
Absorption of Undigested Proteins in Human Beings The Absorption of Unaltered Fish Proteins in Adults Matthew Brunner, M D, and Matthew Walzer, M D, New York	172
Alpha Lobelin as a Respiratory Stimulant William R Marshall, M D, Montreal	180
Toxicity of Novasurol (Merbapnen) Its Action on the Kidney of the Rabbit Benjamin I Johnstone, M B, and H M Keith, M B, Detroit	189
Diabetes A Statistical Study of Two Thousand Cases Henry J John, M D, Cleveland	217
The Effects of Morphine and Ether on the Function of the Kidneys R L Stehle, Ph D, and Wesley Bourne, M D, Montreal	248
The Relation of the Reaction to Epinephrine to the Potassium-Calcium Ratio and Other Ratios W F Petersen, M D, S A Levinson, M D, and Serguis Arquin, M D, Chicago	256
Pancreatic Function I The Quantitative Estimation of Pancreatic Secretion Seizaburo Okada, M D, Enchi Sakurai, M D, Tsunamoto Imazu, M D, and Kwanichi Kuramochi, M D, Tokyo, Japan	270

CONTENTS OF VOLUME 42

AUGUST—Continued

	PAGE
Gastro-Intestinal Reaction to the Emotions The Role of the Vegetative System C W Lueders, M D, Philadelphia	282
Arterial Hypertension and Physical Work Eugene Barath, M D, Budapest, Hungary	297
The Bacteriology of Rheumatic Fever and the Allergic Hypothesis Hans Zinsser, M D, and H Yu, M D, Boston	301
Book Reviews	310

SEPTEMBER, 1928 NUMBER 3

Tapeworm Anemia Therapeutic Observations Raphael Isaacs, M D, Cyrus C Sturgis, M D, and Millard Smith, M D, Ann Arbor, Mich	313
Danger of the Administration of Ephedrine in Heart Failure W A Bloedorn, M D, and P F Dickens, M D, Washington, D C	322
Septicemia Due to a Strain of the Bacillus Mucosus-Capsulatus Group in a Case of Diabetes Mellitus Edward H Mason, M D, and William W Beattie, M D, Montreal	331
Relapsing Febrile Nodular Nonsuppurative Panniculitis Henry A Christian, M D, Boston	338
Pancreatogenous Fatty Diarrhea Report of a Case T E Hess Thavsen, M D, Copenhagen, Denmark	352
Peptone Treatment in Bronchial Asthma Maximilian A Ramirez, M D, New York	368
Chemical Analyses of Blood in Patients Having Senile Cataract Cecil S O'Brien, M D, Iowa City, and Victor C Myers, Ph D, Cleveland	376
Presenile Disturbances of Blood Pressure Eugene Barath, M D, Budapest, Hungary	379
The Value of the Diazo Test on Blood S Milton Rabson, M D, and Lillian Jacobs, A B, New York	386
Functional Insufficiency of the Suprarenal Glands C A Mills, M D, Peking, China	390
Absorption of Undigested Proteins in Human Beings III The Absorption of Unaltered Egg Protein in Adults Henry Sussman, M D, Alexander Davidson, M D, and Matthew Walzer, M D, Brooklyn	409
Peritonitis IV Production of Active Immunity Against the Fatal Outcome of Experimental Fecal Peritonitis Bernhard Steinberg, M D, Toledo, and Harry Goldblatt, M D, Cleveland	415
Relative Lymphocytosis in Hyperthyroidism Val Menkin, M D, Boston	419
Pernicious Anemia Edema and Reduction in Excretion of Water E Meulengracht, M D, Poul Iversen, M D, and F Nakazawa, M D, Copenhagen, Denmark	425
Lordosis as a Cause of Postural Albuminuria Maurice Lewison, M D, Ellis B Freilich, M D, and Oscar B Ragins, M D, Chicago	440
The Dextrose-Tolerance Test Its Use in the Determination of the Severity of Diabetes Mellitus Max Wishnofsky, M D, Brooklyn	443
Book Reviews	453

OCTOBER, 1928 NUMBER 4

Changes in the Fundus Oculi as a Definite Index to Arterial Disease Analysis of One Hundred Cases S A Agatston, M D, New York	455
Scleroderma and Calcinosis Robert H Durham, M D, Detroit	467
The Behavior of the Plasma Chlorides in Obstructive Jaundice I S Ravdin, M D, and M E Morrison, M S, Philadelphia	491
Bronchomoniliasis Report of a Case from Porto Rico W R Galbreath, M D, and Charles Weiss, M D San Juan, Porto Rico	500
Some Observations on the Scapulae of the Chinese H Dabney Kerr, M D, Catonsville, Md	508

CONTENTS OF VOLUME 42

OCTOBER—Continued

	PAGE
The Electrocardiogram in Hypertension Thomas Ziskin MD, Minneapolis	512
Ulceration of the Esophagus Experimental Study Julius Friedenvald, MD Maurice Feldman MD and Waitman F Zinn MD, Baltimore	521
Palm Color Test A Simple Practical Clinical Method for the Diagnosis of Anemia and Plethora W W Duke, MD Kansas City Mo	533
The Parathyroid Glands Their Relationship to the Thyroid with Special Reference to Hyperthyroidism E P McCullagh MD Cleveland	546
Pancreatic Function II The Pancreatic Activity in Diabetes Mellitus Seizaburo Okada MD and Toshio Tzukahara MD Tokyo, Japan	560
The Prevention of Experimental Exudates by the Parathyroid Hormone (Collip) Harry Gold MD, New York	576
Continued Administration of Iodide and Other Salts Comparative Effects on Weight and Growth of the Body P J Hanzlik, MD, E P Talbot AB and E E Gibson AB San Francisco	579
The Inheritance of Migraine William Allan MD, Charlotte, N C	590
Effect of Administration of Medicinal Iron on the Iron Reserve An Experimental Study Charles Spencer Williamson, MD and Paul Ewing, MS Chicago	600
Book Reviews	607

NOVEMBER 1928 NUMBER 5

Xanthomatosis and the Reticulo-Endothelial System Correlation of an Undifferentiated Group of Cases Described as Defects in Membranous Bone-Endothelial and Diabetes Insipidus (Christian's Syndrome) Russell S Rowland MD Detroit	611
Synovial Fluid in Chronic Arthritis Bacteriology and Cytology Claude Ellis Forlner MD New York Alfred R Sharris MD Washington DC and Mary A Poston Baltimore	675
Röntgen-Ray Therapy of the Hypophysis in a Patient with Acromegaly Its Effect on Dextrose Tolerance R Emmet Allen MD and H Lister MD San Francisco	703
Syphilis of the Stomach with Special Reference to Certain Diagnostic Criteria Harry A Singer, MD and Frederick G Diaz MD Chicago	718
Simultaneous Nonsurgical Drainage of the Gallbladder and Intravenous Cholecystography H I Bockus MD and J Gershon-Cohen MD Philadelphia	735
Experimental Obstructive Jaundice III Age Factor in the Production of Bradycardia William C Buchbinder MD Chicago	743
Secretin Not a Hematopoietic Stimulant I T King MD Minneapolis	762
A New Clinical Test for Tissue Thirst William A Thomas MD and Edmund Andrews, MD Chicago	771
Does Commercial Insulin Contain What Has Hitherto Been Called Vitamin B? Charles J Stucky PhD New Haven Conn	780
Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates I - Relationship to Rheumatic Fever Earth I M Irvine-Jones MB St Louis	784
Book Reviews	798

DECEMBER 1928 NUMBER 6

Production of Renal Injury in the White Rat by the Protein of the Diet Dependence of the Injury on the Duration of Feeding and on the Amount and Kind of Protein L H Newburgh MD and A C Curtis, MD Ann Arbor Mich	801
Generalized Granulomatous Lymphadenitis Associated with Diffuse Progressive Fibrosis of the Lung Charles L Coanor MD Boston	822
Experimental Uremia-Uremic Enteritis M H Streicher MD, Chicago	835

CONTENTS OF VOLUME 42

DECEMBER—Continued

	PAGE
A Review of the Technical Methods of Demonstrating the Circulation of the Heart A Modification of the Celluloid and Corrosion Technic Merritt B Whitten, M D, Rochester, Minn	846
Atopy Blood Calcium and Gastric Analysis Leo H Crip, M D, and William S McElroy, M D, Pittsburgh	865
A Comparison of the Effects of General Diets and of Standardized Diets on Tolerance for Dextrose J Shirley Sweeney, M D, Dallas, Texas	872
The Urea Tolerance Test An Index of Renal Function S Edward King, M D, New York	877
Agranulocytosis (Schultz) and the Agranulocytic Symptom Complex William C Hueper, M D, Chicago	893
Ingested Creatine Its Utilization and Rate of Excretion by Arthritic and Normal Subjects F A Cajori, Ph D, L M Wright, M A, and Eleanor Stolz, A B, Philadelphia	901
The Effects of Serums from Normal and from Anemic Persons on the Growth of Seedlings Love Barnett Upjohn, M S, Raphael Isaacs, M D, and Felix G Gustafson, Ph D, Ann Arbor, Mich	909
Bile Acids in Jaundice Ichiro Katayama, M D, New York	916
Distribution of Blood Sugar Between Corpuscles and Plasma in Diabetic and in Alimentary Hyperglycemia Michael Somogyi, Ph D, St Louis	931
The Effect of Parathyroid Extract on Certain Factors Underlying the Production of Edema Abraham Cantarow, M D, and Burgess Gordon, M D, Philadelphia	939
Book Reviews	953

THYROID DISEASE

AN EXPERIMENTAL STUDY ¹

WARREN B COOKSEY, M D

AND

M S ROSENBLATT, M D

DETROIT

The pathogenesis, classification and treatment of the diseases of the thyroid gland continue to be subjects of considerable controversy. Although the etiologic relationship of the thyroid gland to exophthalmic goiter was at one time considered definitely proved, a small group of dissenters have maintained that the thyroid gland cannot be considered more than a single link in the chain of a complicated disease.

Hoover,¹ for example, said

Men write very freely about the excessive flow of internal secretions from a hyperplastic thyroid into the circulation, but this is certainly not true of myxedema and it has never been proved to be true in Grave's disease. In fact, no one has thus far offered anything but inferential or fancied evidence for hyperthyroidism, and that has been so feeble that it will not stand critical inspection.

Israel Bram² went even further, and said

The question involved is not that of a "lump on the neck." We must firmly understand that a subject of Grave's disease is no more a victim of goiter than is a sufferer with typhoid fever one of splenomegaly.

Hyman and Kessel³ said

In our opinion, exophthalmic goitre is a complicated disease, based on a disturbance in the involuntary nervous system, activated by some sympathomimetic factors, of which infection and psychic trauma are examples, and super-activated, if you will, so that there is produced a metabolic upset whose origin is obscure—which may be thyrogenic, but which probably is not.

Solis-Cohen⁴ said

The neurogenic theory of the origin of exophthalmic goiter is the older one, displaced largely through Kocher's work. Some observers, however, of whom

* From the Buhl Laboratory and the Surgical Service of the Harper Hospital.

1 Hoover, C F. Does Hyperplasia Offer any Evidence for the Thyrogenesis of Graves' Disease? *Am J M Sc* **173** 11 (Jan) 1927.

2 Bram, Israel. The Prevention of Exophthalmic Goiter, *Endocrinology* **7** 415 (May) 1923.

3 Hyman, H T, and Kessel, L. Exophthalmic Goiter and Involuntary Nervous System, *J A M A* **85** 1017 (Oct 3) 1925.

4 Solis, Cohen, S. In discussion of Hyman and Kessel (footnote 3).

I am one, have held to it throughout. We look on the goiter and the symptoms of dysthyroidism as incidents and epiphenomena. They may or may not be present.

The point of view adhered to by many of the clinicians who do not favor the thyrogenesis of exophthalmic goiter is that one is dealing with a group of patients who by hereditary and acquired predisposition become susceptible to an exciting cause capable of setting up an improper balance of the autonomic and endocrine systems.

On the other hand, the advocates of the thyrogenesis of exophthalmic goiter are numerous. Most surgeons feel that the removal of the thyroid gland is indicated in exophthalmic goiter and in most cases are able to hold out great hopes for a complete cure. Richter,⁵ for example, reported 100 cases in which the patients were operated on for "thyrotoxicosis" and claims that 99 of the patients were relieved of hyperthyroidism after operation. He says: "Aside from all question of the exciting cause, the immediate source of the clinical syndrome called exophthalmic goiter lies entirely within the thyroid gland. Its removal is incompatible with the continued existence of the disease in its various forms."

Crile⁶ said:

In hyperthyroidism, the thyroid gland is the druggist, an extraordinary druggist, a tireless druggist, who day and night is manufacturing and turning into the circulation the exciting hormone." He further says:⁷ "Taking into account the slight primary risk and the promising immediate and remote results of operation, we now consider in the case of hyperthyroidism as in that of appendicitis that the indication for operation is diagnosis."

In these introductory remarks, we have used the term exophthalmic goiter because we feel that the syndrome of exophthalmic goiter gives a clearer picture to most clinicians than any other term we might have selected. However, obviously the question of hyperthyroidism is not solely concerned with the syndrome of exophthalmic goiter. Hypersecretion of the thyroid gland is just as much a question in those cases of so-called "thyrotoxicosis" in which the syndrome of exophthalmic goiter is not present or is incompletely present. It is our opinion that it is impossible to distinguish any reliable pathologic differences in the various types of so-called hyperthyroidism, no matter what the mode of onset or the presenting clinical picture.

⁵ Richter, H. M. Thyroidectomy, Its Relation to the Cure of Thyrotoxicosis, *J. A. M. A.* **88** 888 (March 19) 1927.

⁶ Crile, G. W. Certain Problems in the Treatment of Diseases of the Thyroid Gland, *J. A. M. A.* **83** 813 (Sept 13) 1924.

⁷ Crile, G. W. Surgical Treatment of Hyperthyroidism, *South. M. J.* **16** 459 (June) 1923.

In view of the conflicting opinions presented, it was our desire at the onset of this investigation to attempt to obtain more conclusive proof or disproof regarding the question of altered or excessive thyroid secretion in exophthalmic goiter and allied diseases. In the past, numerous attempts have been made to settle this question, and in reviewing the literature we found rather conflicting data. Hara⁸ reported that the blood in cases of exophthalmic goiter exerted an effect like thyroxin in increasing metabolism. On the other hand, Wilson and Kendall⁹ found that the thyroid gland in cases of toxic goiter contained but one-fifteenth to one-twentieth as much thyroxin as found in patients with normal glands. Hunt¹⁰ reported that the acetonitril test for thyroid secretion was positive in the blood from patients suffering with exophthalmic goiter, whereas in blood from normal patients the test was not positive. From the experimental data derived from the various commercial sources using desiccated thyroid preparations or thyroid extracts, it has become clear that animal thyroid preparations vary in potency, and that the variation is proportional to the iodine content of the glands. But the thyroid gland in exophthalmic goiter has a noticeably low iodine content. Jolin,¹¹ Wells,⁵ Weir,¹² Oswald¹³ found that the physiologic activity of thyroglobulin obtained from goiters was the same as that obtained from patients with normal glands, except that it was weaker in direct proportion to the amount of iodine it contained, being free from effect in the total absence of iodine.

Feeding experiments in which goitrous glands from human beings were used seem surprisingly rare. Lenhart¹⁴ fed thyroid glands from people to tadpoles including glands affected by simple and exophthalmic goiters and he stated that they all acted alike qualitatively. Abderhalden and Schiffman¹⁵ also conducted feeding experiments, and they too, con-

8 Hara, in Wells H G. Chemical Pathology, Philadelphia, W B Saunders Company, 1925, p 696

9 Wilson and Kendall. The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, *Am J M Sc* **151** 79, 1916

10 Hunt Reid. Acetonitril Test for Thyroid and of some Alterations of Metabolism, *Am J Physiol* **63** 257, 1923

11 Jolin, in Wells, H G. Chemical Pathology, Philadelphia, W B Saunders Company, 1920, p 604

12 Weir, J F. Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, *Am J M Sc* **169**.860, 1925

13 Oswald. Ueber die Wirkung der Schilddruse auf den Blutkreislauf, *Arch f d ges Physiol* **164** 506, 1916

14 Lenhart, C H. The Influence on Tadpoles of Feeding Desiccated Thyroid Gland, *J Exper Med* **22** 739, 1915

15 Abderhalden and Schiffman. Studien ueber die von einzelnen Organen hervorgebrachten substanzen mit spezifischer Wirkung, *Arch f d ges Physiol* **195** 167, 1922

cluded that the physiologic activity of preparations from goitrous glands was the same as that from normal glands, and that it varied directly with the iodine content. These experiments have not seemed entirely conclusive to us, however, and in view of the fact that one of us (W B C),¹⁶ had previously conducted thyroid feeding experiments for another purpose, we decided to repeat this work on a more comprehensive scale.

The basis of the experimentation is derived from the pioneer work of Gudernatsch,¹⁷ in which he demonstrated that tadpole larvae when fed thyroid gland preparations would undergo complete metamorphosis in a much shorter time than normally. Subsequent work has not only confirmed this fact, but demonstrated that the change in form by the larvae is a direct expression of the stimulation of metabolism (Lenhart¹⁴).

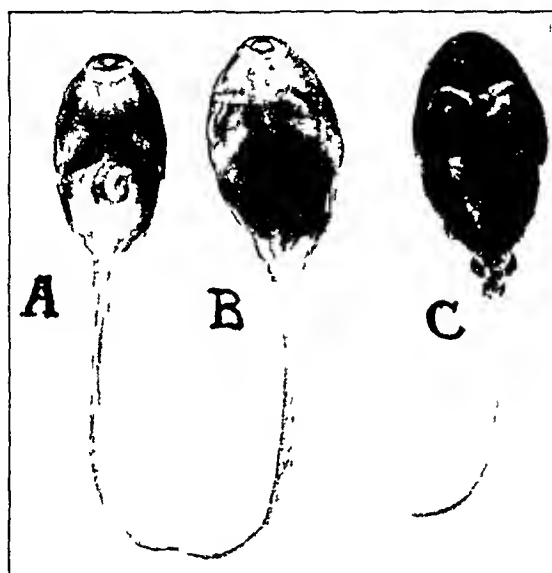


Fig 1—Normal metamorphosis of amphibian larva, *Rana Pipiens*. A shows tadpole aged 2 weeks, B, 3 weeks, C, 5 weeks. Note the appearance of posterior limb buds in C and the disappearance of simple coiled intestine.

Swingle,¹⁸ by his admirable work in this field, pointed out the influence of organic iodine and allied substances on tadpole metamorphosis and warned against the tadpole test in determining the thyroid potency of commercial preparations. By using proper controls and by a comparison of iodine contents, we feel that Swingle's suggestions are not applicable in the following experiment.

16 Cooksey, W B. The Influence of Thyroid Feeding on the Brain of *Rana Pipiens*, *Endocrinology* 6 393 (May) 1922.

17 Gudernatsch, J F. Feeding Experiments on Tadpoles, *Am J Anat* 15 431, 1914.

18 Swingle, W W. Is the Tadpole Test for Thyroid Valid? *Endocrinology* 8 832 (Nov) 1924.

EXPERIMENTAL WORK

In conducting the experiment, we used the thyroid glands from thirty persons operated on for goiter over a period of two months. These glands were taken from the operating room to the laboratory as quickly after their removal as possible. In the laboratory, the gland was stripped of fatty and fibrous tissue, and after suitable sections for microscopic study had been removed, the gland was cut into small pieces, care being used not to lose any of the juice of the tissue. The thyroid which had been cut was spread on large watch glasses, carefully weighed and then placed in a vacuum desiccator over calcium chloride. The glands were desiccated at room temperature and were usually dry in twenty-four hours, although for uniformity they were left in the desiccator four days. After desiccation, the glands were placed in a large mortar and ground into a fine powder. The fresh and dry weight was

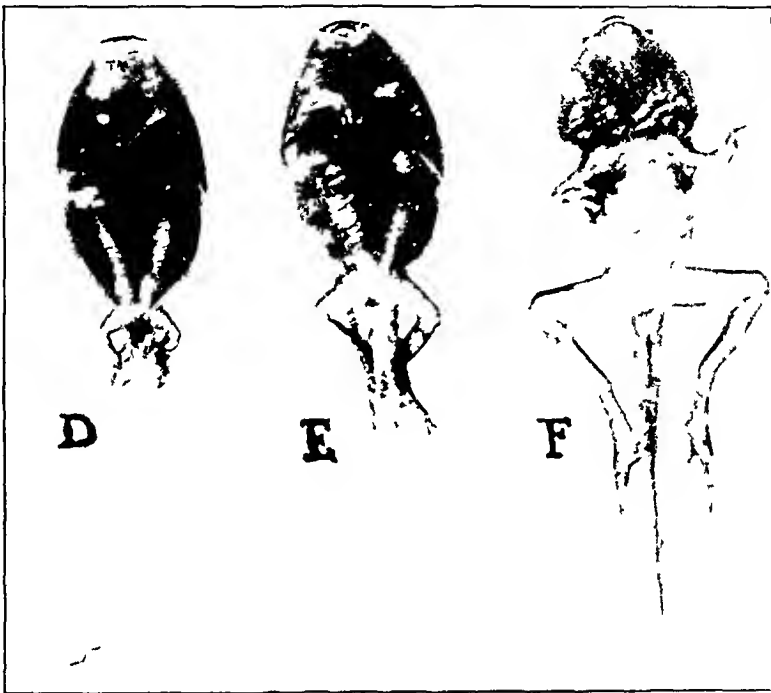


Fig 2—Normal metamorphosis continued. *D* shows tadpole aged 6 weeks, *E*, 7 weeks, *F*, 9 weeks. Note the limb buds, shortening of the tail, and adult appearance of the snout. The latter occurs as the gills disappear.

recorded in each case. By Kendall's method,¹⁹ the iodine content was determined, each determination being checked at least twice.

The larvae used were hatched from fresh eggs of *Rana pipiens* obtained through the courtesy of the University of Michigan biologic department. Tadpoles of similar age and size were carefully selected, and each lot was given a control period of from five to seven days. The control food consisted of one part egg yolk, two parts powdered clover leaves and eight parts of flour mixed together in a paste and spread out in a thin layer to dry. This food, consisting of thin flakes, was easily ground to small pieces suitable for feeding even extremely small larvae. The food which contained thyroid was prepared in a similar way, each ingredient being carefully weighed and each preparation containing

¹⁹ Kendall, E. C. Determination of Iodine in Connection with Studies in Thyroid Activity, *J Biol Chem* **43** 149, 1920, **19** 251, 1914.

sufficient thyroid powder to be exactly equivalent to 4 Gm of fresh gland. The food was fed to the larvae once daily, each bowl being the same size and containing the same number of tadpoles, while a similar amount of food was fed each lot. The complete feeding experiment was repeated three times, tadpoles of various ages being used for a comparative study.

The results of our experiments are shown in the table. However, there are several important details that warrant further elaboration.

By reference to the table, it is obvious that, except for slight variation, glands removed from patients who bore marked clinical signs of

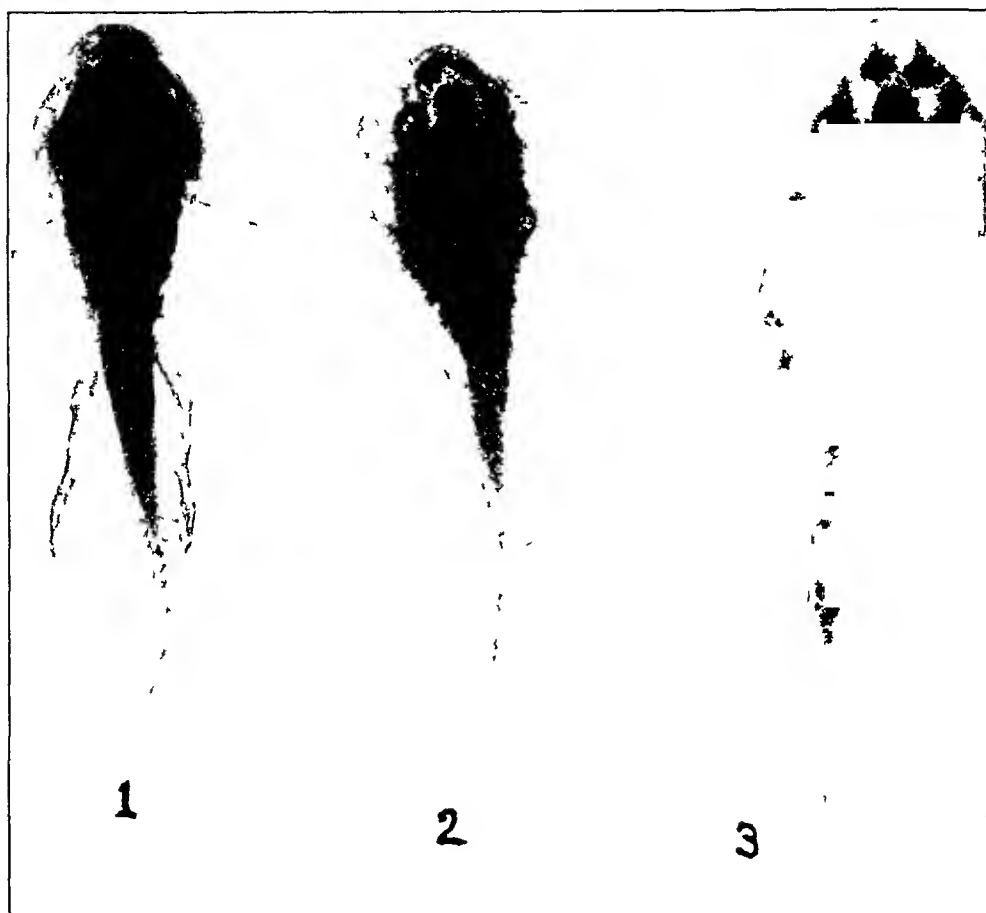


Fig 3—Acceleration of the metamorphosis by thyroid feeding for eight days in larvae aged 4½ weeks. 1 is a representative specimen from lot fed exophthalmic goiter gland, gland from case 4 being used, 2, specimen from lot fed normal human gland, 3, specimen from lot fed normal food. Note how nearly complete is the metamorphosis of larva 1, which was fed the goiter gland.

thyroid toxicity, namely, tachycardia, nervousness, loss of weight, etc., were able to produce a parallel situation in the experimental larvae, that is, extremely toxic goiter glands produced a more marked acceleration of larval metamorphosis than was produced by the less toxic or normal gland. This will be more clearly seen by reference to figures 4 and 5, which represent cases 4 and 7 with their controls.

Representative Specimens of the Experiment

Case	Weight of Gland	Iodine Content	Diagnosis	Basal Metabolic Rate	Degree of Involution	Duration of Symptoms	Reaction of Postoperative	Clinical Activity of Case	Spectral Analysis of Gland			Comment	
									Spectral Analysis of Gland				
									Lot 1	Lot 2	Lot 3		
2	19.6	2.21	Normal human gland	1.54	Advanced	Unoperated 15 years, symptoms 1 year	Moderate	IV	III	III	IV	Normal gland obtained at autopsy	
3	70.9	1.21	Old adenoma toxic	1.53	Moderate	2 1/2 years	Death in storm	IV	IV	III	III	IV	Developed exophthalmos 3 weeks before operation, gland was degenerated in center
5	52.1	2.06	Late primary hyperplastic	1.76	Moderate	1 year	Very slight	I	I	II	II	I	Had severe hemorrhage 1 hour postoperative, died in storm 15 hours postoperative
6	54.5	1.58	Primary hyperplastic Old adenoma toxic	1.62	None	Unoperated 12 years, symptoms 1 year	Severe	III	II	II	III	III	Weakness the only symptom
7	35.0	3.02	Primary hyperplastic	1.10	Advanced	9 months	Very severe	IV	IV	IV	IV	IV	Central portion of gland degenerated, microscopic hemorrhages
8	32.3	1.76	Primary hyperplastic	1.52	Very slight	3 to 4 months	Severe	III	II	II	III	III	Typical rapid primary hyperplasia with lymphadenitis. Single lobectomy
9	25.1	1.01	Primary hyperplastic	1.80	Advanced	1 year	Very slight	III	IV	III	III	II	Single lobectomy 3 months previous with much relief
10	21.5	1.75	Primary hyperplastic	1.71	Moderate	1st operation	Slight	II	I	I	I	I	Operation and lobectomy 3 months previous with much relief
11	11.0	1.06	Colloid adenoma	1.51	Complete	Unoperated 20 years, symptoms 1 year	Very slight	I-II	I	I	I	I	Gland cystic with much central degeneration
12	18.0	5.11	Late primary hyperplastic	1.55	Moderate	1 year	Very severe	IV	IV	IV	III	III	Single lobectomy
13	20.2	1.01	Primary hyperplastic	1.25	Slight	1 year	Very slight	I	0.1	I	0-1	0-1	Had much rest, iodogen in treatment and compound solution of iodine
14	31.1	2.51	Primary hyperplastic Simple colloid (2)	1.20	Complete	1 to 5	Slight	I	I	I	I	I	Thyroid gland, diagnosis not clear

* Note how closely the clinical activity of the glands used parallels the experimental activity, in the larvae fed on thyroid. All weights are in grams of fresh gland and iodine contents are in milligrams of iodine per gram of dry gland. Lot 1 represents larvae 10 days old at the beginning of the feeding, lot 2, larvae 11 days old, and lot 3, larvae 20 days old.

REPORT OF CASES

CASE 4—A negro, aged 27, had had symptoms of exophthalmic goiter for two and one-half years. He was extremely nervous, had marked tachycardia, had lost 50 pounds (22.7 Kg) in weight and had exophthalmos, tremor and lid lag. He had a rather severe hemorrhage two hours after operation, which was con-

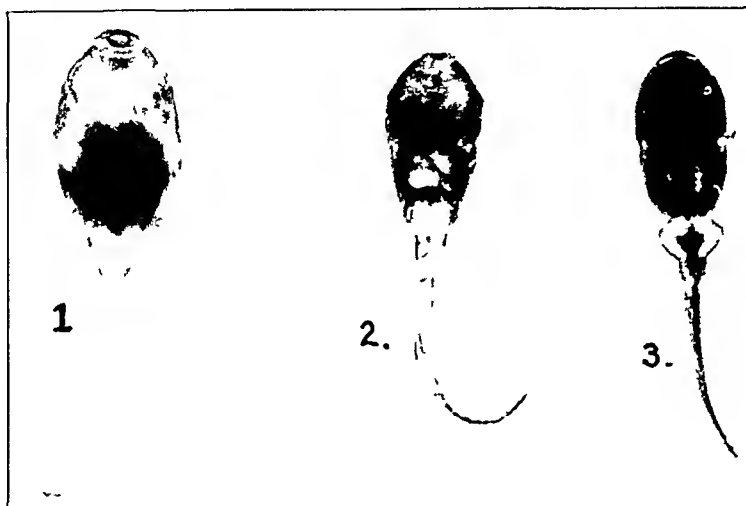


Fig 4—Representative specimens from lot 3 of experimental larvae. Tadpoles were 26 days old and were fed experimental food for seven days. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 4. Note the anterior and posterior limb buds in 3 and the close proximity to adult form.

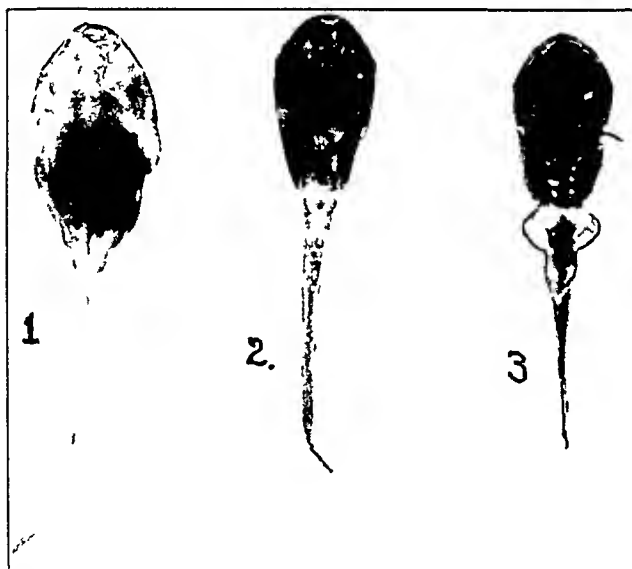


Fig 5—Representative specimens from lot 3 of experimental larvae. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 7. Note the almost complete adult form of tadpole 3.

trolled, but he died fifteen hours later in a typical thyroid storm. A diagnosis of primary hyperplastic goiter, with the syndrome of exophthalmic goiter was made. The tadpoles from the lots fed glands from patients nos 3 and 12 showed a similar acceleration of development.

Figures 4 and 5 show that practically a complete change to adult form occurred in those larvae to which goiter glands were fed. Both anterior and posterior limb buds are present, the tail length is decreased, and an adult form is obvious. Since in all the feeding experiments, exactly the same amount of fresh gland was used in each lot, one must conclude that the thyroid gland in these cases actually contains more active principle than is normal.

Case 11 is an example in which the thyroid from a case of nontoxic goiter was used (figs 6 and 7).

CASE 11—A woman, aged 31, had had a large thyroid for twenty years. Four years ago, during her last pregnancy, the thyroid increased in size, and she was slightly nervous and tired easily.

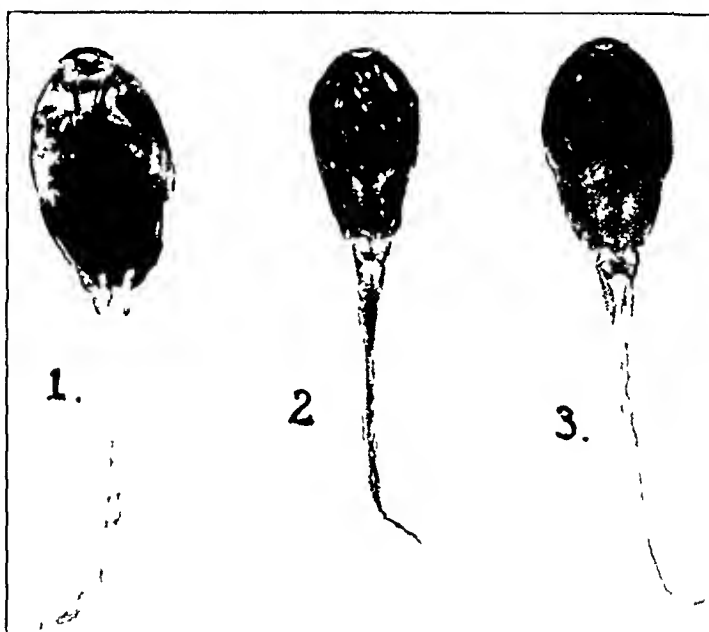


Fig 6—Representative specimens from lot 3 of experimental larvae. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 11. Note that tadpole 3 is little changed from the specimen fed normal food, the tail is not shortened, the snout is little changed, and posterior limb buds are just appearing.

She had never had tremor or exophthalmos, or lost weight and her blood pressure was normal. Both lobes of the gland weighing 134 Gm were removed, and she had a slight postoperative reaction. A diagnosis of colloid adenoma was made (fig 6 and case 11 in table, see also cases 13 and 14 in table).

Apparently these glands were not able to accelerate tadpole metamorphosis greatly, for the larvae were not even as fully developed as were the ones which had been fed with normal human glands.

Figure 8 and cases 3 and 6 in the table are examples of toxicity arising on the background of old adenomas.

CASE 6—A woman, aged 57, first noticed enlargement of the thyroid gland twelve years before admission to the hospital. For one year she had had symptoms

which consisted of nervousness, palpitation and tremor. She had lost 12 pounds (5.4 Kg) in weight, and her basal metabolic rate was + 62 per cent and + 32 per cent before operation. She was extremely toxic. A large, friable gland was removed, which weighed 81.5 Gm, and in the center of which was a large area of degeneration. Microscopic examination showed numerous hemorrhages. She had a severe postoperative reaction.

As seen by the figure, this gland was able to accelerate larval metamorphosis almost as much as the gland in case 4, in which there was a primary hyperplastic goiter with the syndrome of exophthalmic goiter.

The iodine content of normal thyroid gland preparations has been shown repeatedly to be closely correlated with the activity of the preparation. But in these experiments, we have found that the iodine content is

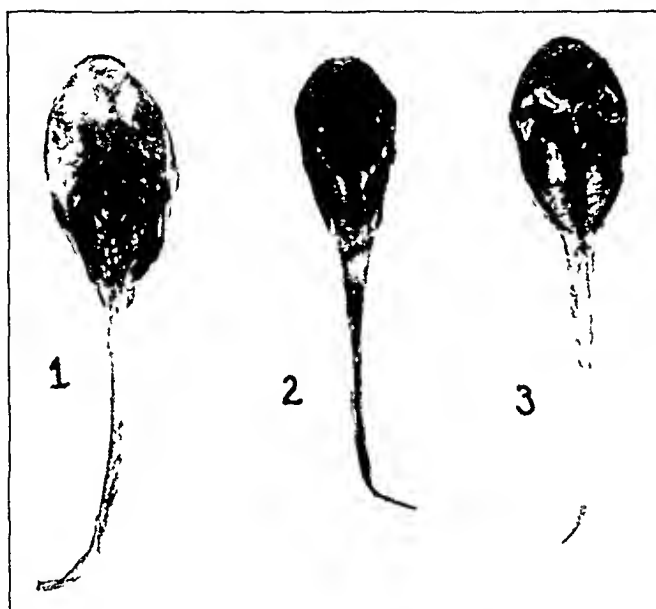


Fig 7—Representative specimens from lot 3 of experimental larvae. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 13. The patient in case 13 had a mild primary hyperplastic goiter and had had much rest, roentgen-ray treatment, and compound solution of iodine. Note that 3 shows little change over 1, which was not fed thyroid.

by no means the only factor involved in abnormal gland preparations. It must be considered that practically all of the patients from whom these glands were removed had been given compound solution of iodine. For that reason, the iodine content of the glands is abnormally high. One might, therefore, expect certain abnormal factors to be present in the feeding results due to the organic iodine itself. However, there is not one exception to the rule that the glands removed from clinically toxic cases are able to produce marked acceleration of metamorphosis regardless of the iodine content of the gland used. Cases 4, 7 and 12 illustrate this fact extremely well, for regardless of the low iodine con-

tent in case 4 experimentally it proved just as active as case 7 or 12 in which the iodine content was much higher. Also in cases 9 and 13, the goiters are of the primary hyperplastic type because of previous operation or roentgen-ray treatment plus much rest and iodine a low clinical toxicity is present. Although these glands had a high iodine content they were not able to exert a pronounced effect on larval metamorphosis.

It will be noted that those glands with a high iodine content were more toxic for lots 1 and 2 of the tadpoles than they were when fed to lot 3. This was evident by the extreme emaciation and early deaths of the larvae of lots 1 and 2 when active glands with high iodine contents were fed to them. This is due to the fact that lots 1 and 2 represented

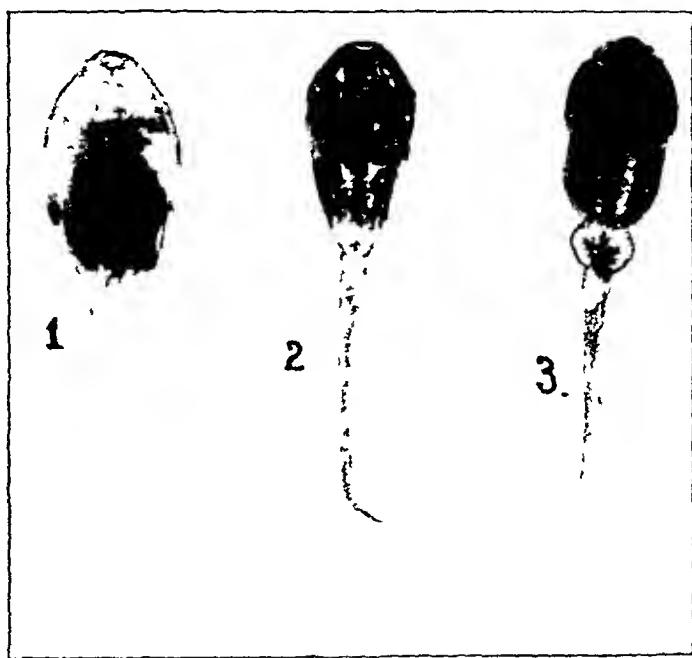


Fig 8—Representative specimens from lot 3 of experimental larvae. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 6.

larvae only 10 and 14 days old respectively, while the tadpoles used in lot 3 were all 26 days old. As also reported by other workers the younger larvae are much more easily killed by thyroid and organic iodine than the older larvae, hence much more reliable data may be obtained when the older tadpoles are used since in them the larvae are able to proceed to more complete changes before toxic effects are manifest.

In order to check further the question of iodine content, food was prepared by the addition of iodocasein (Mulford) to the food otherwise prepared as before. Sufficient iodocasein was added to each preparation so that the total organic iodine was 5.34 mg per gram of thyroid. This gave a value, such that each preparation contained the amount of iodine

present in gland no 12 in which the iodine content was highest. This food was now fed as before to a separate lot of tadpoles. We were unable to detect the slightest difference in the tadpoles fed this food from those in lot 3 who were started at about the same age, but who were fed the thyroid preparation without the addition of extra iodine.

In conclusion, we feel that these experiments have shown by biologic test that the thyroid gland in exophthalmic goiter contains quantitatively more active principle than is present in either the normal human thyroid or the thyroid of patients with less toxic goiter. They have further shown that the amounts of active principle demonstrable in the gland by these tests on amphibian larvae is directly proportional to the clinical activity of the patients from whom the glands were derived. Certain glands removed at operation apparently contained large amounts of this

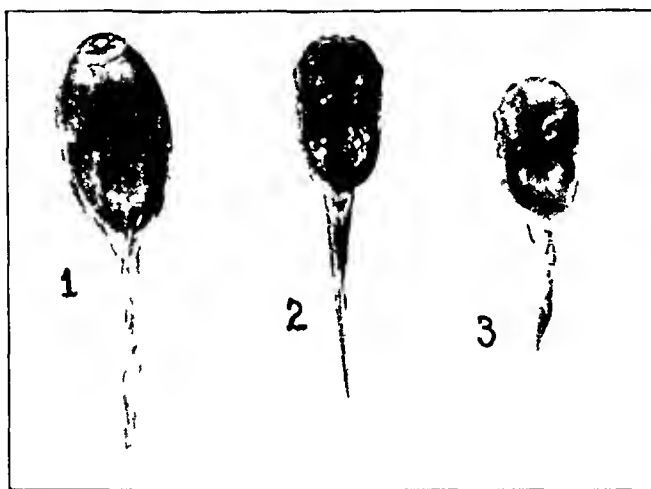


Fig 9—Representative specimens from lot 2 of experimental larvae. The tadpoles were 14 days old and were fed the experimental food for eight days. 1 shows specimen fed normal food, 2, specimen fed normal human thyroid, 3, specimen fed goiter gland from case 7. Note the emaciation, shortened tail and change of intestinal form in the larvae fed on thyroid. At this age many of the larvae die from the toxic effects before metamorphosis has proceeded far.

active principle, while others contained smaller amounts, and some apparently contained less than the normal amount. There has not been a direct correlation between this test and the iodine content of the glands, thus showing that in these goitrous glands iodine content is not a reliable measure of activity. While the majority of these patients had been given a compound solution of iodine, it had been given in variable amounts and for various lengths of time, and a few had received practically no iodine. This is also shown by the degree of involution of the glands. If the contention is correct that a compound solution of iodine causes a binding of thyroid secretion in the gland, we should expect those cases which had been completely iodized and which had shown complete

glandular involution to be most potent experimentally. This was not the case and as some have contended it is probably due to the fact that the large amount of colloid material evident by microscopic examination in these involuted glands is not the active thyroid secretion, but stored colloid. Perhaps the storage of this inactive colloid temporarily inhibits secretion of the true thyroid principle. Certainly there was no correlation, as far as we could see, between the degree of involution change and the experimental activity.

SUMMARY

1. The question of excessive thyroid secretion in exophthalmic goiter and allied diseases is discussed, and the various claims for and against hyperthyroidism are presented.

2. Feeding experiments were conducted in which various types of goitrous glands from human beings were fed to tadpole larvae. There is evidence from these experiments that thyroid glands from clinically active cases of goiter actually contain more active thyroid principle per unit weight than the normal thyroid. Other goitrous glands contained less active principle by this biologic test, and the amounts were directly proportional to the clinical activity of the patient. Old non-toxic adenomas contained less active principle per unit weight than normal, while one gland which had had much roentgen-ray treatment and rest also contained less active principle per unit of weight.

3. By these experiments, hypersecretion of the thyroid gland in exophthalmic goiter and other clinical thyrotoxic cases seems definitely proved.

CARDIAZOL

SOME EXPERIMENTAL EFFECTS OF THIS DRUG ON THE CARDIORESPIRATORY MECHANISM ¹

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AND

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Much has been written of late, especially in the continental medical journals, as to the value of cardiazol (penta-methyl-tetrazol) It has been recommended especially in cases of acute cardiovascular collapse and respiratory failure Glowing reports are appearing of its use in varied conditions, such as pneumonia, surgical shock, intrapartum asphyxia, auricular fibrillation, angina pectoris, diabetic coma, scopolamine depression and other conditions The bulk of these reports, however, are of poorly controlled clinical observations made on a small number of cases, usually from three to six, when other stimulants had previously been given It is our purpose in this paper to give a short summary of the pharmacology of cardiazol and to report some experimental work concerning the points for which it is most recommended

Camphor has long been used as a cardiac stimulant, especially in acute conditions and in moribund states Lewin,¹ in 1890, and Schwalb,² in 1912, found it to be a depressant Joachimoglu,³ in 1916, was unable to substantiate previous favorable reports, they also believed that it was a cardiac depressant Heathcote⁴ found that the administration of camphor intravenously produced a sharp fall in the blood pressure, and concluded that "there is no convincing pharmacologic evidence that camphor possesses any value whatever as a cardiac or circulatory stimulant" Sollmann⁵ felt that its effects were inconstant and unreliable, and that no conclusions could be drawn from experimental work on animals Cushney⁶ said "There is no reason to believe that camphor, in even the largest therapeutic doses, has any effect after absorption

¹ From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine of the Harvard Medical School

1 Lewin, A Arch f exper Path u Pharmacol **27** 226, 1890

2 Schwalb, H Arch f exper Path u Pharmacol **70** 70, 1912

3 Joachimoglu, G Arch f exper Path u Pharmacol **80** 259, 1916

4 Heathcote, R A J Pharm & Exper Therap **21** 177 (April) 1923

5 Sollmann, T A Manual of Pharmacology, Philadelphia, W B Saunders Company, 1922, p 493

6 Cushney, A R Pharmacology and Therapy, Philadelphia, Lea & Febiger, 1924, p 72

except a slight dilatation of the skin vessels" Marvin and Soifer⁷ arrived at similar conclusions from clinical observations

An occasional striking result, however, is apparently obtained from the use of camphor, and investigation has been continued in an attempt to find some active principle in the drug. Most organic groupings having an effect on the heart have been found to be limited to the organic nitrogen compounds. The aliphatic amines have little if any effect, and most of the aromatic amines are too toxic for prolonged use.⁸ The imadazol ring seems ineffective, but little has been done with the tetrazol group.

Schmiederberg and Meyer⁹ felt that since camphor is insoluble and is suspended in oil, the irregular therapeutic responses were due to the variability of absorption, hence an inconstant dosage. Various forms and isomers of camphor have been investigated. Gottlieb and Schuleman¹⁰ synthetically produced a camphor substitute, 3 methyl — 5 isopropyl — 2-3 cyclohexanon (Hexeton-Bayer), soluble in 20 per cent aqueous solution of sodium salicylate. Schmidt and Hildebrandt¹¹ found that camphor effects were not limited to the members of the terpene group soluble with difficulty, but could be produced by several compounds of the nitrogen-polymethylene series. One of this series Schmidt¹² developed by the action of two molecules of hydrazoic acid on cyclohexanon, giving the compound sold under the name Cardiazol. Schmidt has claimed it to be pentamethylentetrazol.*

Schmidt and Hildebrandt¹² found cardiazol stable to heat, readily soluble, quickly absorbed and not cumulative. The extraordinary absorptive quality rendered it practically as effective when given subcutaneously as when given intravenously, as regards dosage and reaction time. They reported a stimulating effect on the heart of the frog, rat and rabbit, both in normal and in depressed states (chloroform) when isolated and intact hearts were used. Respiration depressed by morphine was improved, and they considered that the cortex of the brain was "powerfully stimulated by cardiazol." They, therefore, concluded that cardiazol was distinctly an improvement on camphor. Experimentally, they found a

* In the preliminary report of the Council on Pharmacy and Chemistry (J. A. M. A. **90** 2019 [June 23] 1928) it was recommended that the name Metrazol be used instead of "Cardiazol."

7 Marvin, H. M., and Soifer, J. D. Value of Camphor-in-Oil as a Cardiac Stimulant, J. A. M. A. **83** 94 (July) 1924

8 Wolf and Sherman. Clin. Med. **33** 8 (Aug.) 1926

9 Schmiederberg and Meyer. Ztschr. f. Phys. Chem. **3** 422, 1924

10 Gottlieb, R., and Schuleman, W. Deutsche med. Wchnschr. **49** 1536 (Dec.) 1923

11 Hemmerling. Deutsche med. Wchnschr. **51** 1618, 1925

12 Schmidt, K. F., Hildebrandt, F., and Krehl, U. Klin. Wchnschr. **4** 1678 (Aug. 27) 1925

definite effect within from thirty to sixty seconds when given intravenously, and in from one to three minutes when given subcutaneously. Toxic effects were obtained in rats with a dose of 10 mg per hundred grams of body weight and lethal effects with 15 mg. Rabbits showed toxic manifestations with from 10 to 15 mg per kilogram of body weight and convulsions with doses of from 20 to 30 mg when given intravenously, and from 30 to 40 mg per kilogram when given subcutaneously. Eichler and Hildebrandt¹³ found the blood pressure to be slightly depressed and the heart rate slightly decreased.

Stross¹⁴ found that the heart of a normal frog was unaffected by cardiazol, and that large doses had a chronotropic and inotropic action, the heart finally stopping in diastole. He depressed the action of the heart by several methods, including that used by Schmidt and Hildebrandt (chloroform) and concluded that cardiazol was frequently of help, but not nearly as effective as either caffeine or epinephrine. After cardiazol had failed, cardiac arrest produced by potassium and ox gall was overcome by epinephrine, on the one hand, and by caffeine, on the other. He found, however, a marked increase in the blood pressure, which was not obtained in the decerebrate animal. Schoen¹⁵ experimentally caused depression in rabbits until the vestibular reflex was lost, and found that cardiazol was beneficial, it was not beneficial, however, if the depression was carried much deeper.

In an attempt to clarify some of the rather conflicting reports, a series of experiments on cats has been carried out in this clinic to determine the toxic and lethal doses. Effects on the action of the heart, blood pressure and respiration were then observed in the anesthetized animal, finally, the same observations were made in various experimentally produced states of depression.

EXPERIMENTAL TECHNIC

Thirty-five adult cats were used, and several experiments were performed with many. They were placed on an animal board in the dorsal position, and carried under light ether anesthesia. The right fore leg and the left hind leg were shaved, and the customary lead II electrocardiograms were made. The left femoral artery and vein were exposed, and 0.1 Gm of heparin¹⁶ was dissolved in 2 cc of physiologic sodium chloride solution and injected intravenously. A cannula was inserted in the left femoral artery and connected with a mercury manometer by means of a rubber tube containing 3 per cent acacia solution under slight pressure. Clamps between the cannula and the manometer were then

13 Eichler, O, and Hildebrandt, F. *Arch f exper Path u Pharmacol* **116** 110, 1926.

14 Stross, William. *Arch f exper Path u Pharmacol* **114** 177, 1926.

15 Schoen, R. *Arch F exper Path u Pharmacol* **113** 257, 1926.

16 Gordon, B, Matton, M, and Levine, S. A. *J Clin Investigation* **1** 497 (Aug) 1925.

removed, and a graphic record of the arterial pressure was traced. A pneumograph was placed about the cat's chest and connected with a tambour, and a similar tracing of the respiration was recorded. Medication was given intravenously and subcutaneously. Ten per cent solution of cardiazol (Knoll¹⁷) in ampules was used throughout this study. A neutral 1 per cent solution of quinidine sulphate (U S P) in doses of from 6 to 30 mg per kilogram was employed to depress respiration and heart action and to lower the blood pressure in one series of experiments,¹⁸ while 0.5 per cent solution of sulphuric acid was used for the same purpose in another.¹⁸ Caffeine sodiobenzoate in physiologic sodium chloride solution was given in doses of 10 mg per kilogram.

TOXIC, SUBLETHAL AND LETHAL EXPERIMENTS

Cardiazol was given to anesthetized animals in doses of from 1 to 15 mg per kilogram. Such doses go well below and above those recommended for clinical use. In this group of eight animals, no favorable respiratory, cardiac, blood pressure or electrocardiographic changes were noted, but frequently, a decided depression of blood pressure and heart

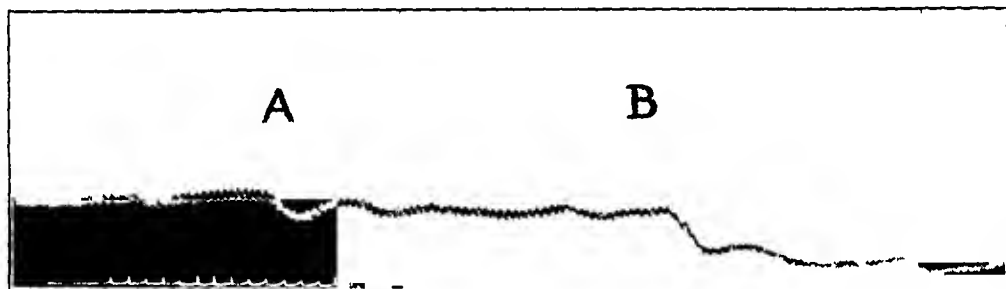


Chart 1—In this and the following charts the upper tracings show respiration and the lower show blood pressure. At the bottom, time is indicated in intervals of ten seconds. In the other figures, although time is not indicated, the same measurements obtain. Cardiazol, 15 mg per kilogram was given intravenously at A, and 10 mg per kilogram at B. Note that respiration is not affected except by a definite slowing with the second dose. The blood pressure fell slightly with the small dose and more markedly with the larger dose, the total fall was from 160 to 136 mm of mercury. The pulse amplitude markedly diminished.

action occurred (chart 1). Total amounts as large as 480 mg per kilogram were without a toxic effect when given in small divided doses (from 3 to 5 mg per kilogram) at intervals of six minutes. This indicates that there is little if any accumulation, for much smaller amounts were lethal when given in single doses.

Toxic manifestations developed constantly within from forty-five to ninety seconds after intravenous administration, with doses of about 35 mg per kilogram. Fine fibrillary twitchings appeared first about the

17 We are indebted to E. Bilhuber of New York for a liberal supply of this drug that was used in this investigation.

18 Bayliss, W. M. Intravenous Injection in Wound Shock, *Brit. M. J.* **2** 553, 1918.

lips, the eyes and in the legs. Various degrees of generalized muscular spasticity frequently occurred and occasionally a convulsion of varying severity and duration. There were peculiar changes in the respiration. At first, there was a deep inspiration accompanied by generalized muscular spasms, and the respiration was held in this position (chart 2). After from sixty to ninety seconds, shallow and rapid respiratory phases ensued, resulting in embarrassed aeration with cyanosis of the lips and tongue. This condition gradually passed off, usually restoring the respiration to a normal rate and amplitude in from twelve to eighteen minutes. These experiments showed that the doses from 35 to 70 mg per kilogram were toxic, but not lethal. The severity of the toxic symptoms varied with the amount injected.

Single doses of 80 mg or more per kilogram were lethal in every case (seven experiments), whether given intravenously or subcutaneously. The animals showed the usual toxic symptoms about a minute after administration, then quieted down, only to resume terrific tonic convulsions about one and one-half hours later, these convulsions were



Chart 2—This chart illustrates the toxic results from 35 mg per kilogram of cardiazol given at *A*. Note first a cessation of respiration at *B*, animal held breath in deep inspiration and showed fibrillary twitchings. The respiration was regular. From *C* to *D*, there were convulsions. The animal recovered.

fatal. The blood pressure was decreased in varying amounts, and the only significant fact noted in the electrocardiographic tracings was a slight slowing of the heart rate (an average of from 165 to 150) and an occasional inversion of the T wave. Postmortem examination showed a rigid, outstretched animal, with much froth about the nostrils and mouth. The intestines were in a spastic state, and the heart was arrested in systole. Gross changes of the central nervous system were not noted.

EXPERIMENTAL COLLAPSE

A sharp fall in the blood pressure of from 60 to 70 mm of mercury, produced by neutral quinidine sulphate in doses of from 6 to 9 mg per kilogram, was not benefited by cardiazol. Doubling the foregoing doses of quinidine produced a decrease in the rate and amplitude of respiration in addition to the customary fall in blood pressure. The patient was not improved by the use of cardiazol (chart 3). Not only was there failure to support respiration and blood pressure, but frequently the depression

was made definitely worse by cardiazol. In fact, occasionally the depressed state from which recovery was to have been expected proved to be fatal after even a small dose of cardiazol. Such an experience was well illustrated in chart 4. Here a moderate depression of respiration and blood pressure was first obtained by the administration of 5 mg per kilogram of quinidine, from which state a complete recovery ordinarily takes place in from twelve to fifteen minutes. In this instance, the customary recovery was taking place when cardiazol was given. The return of blood pressure was almost immediately arrested and followed by a cessation of respiration, slight convulsion, failure of heart action and death.

Doses of 30 mg per kilogram of neutral quinidine sulphate produce a fall in blood pressure of 100 mm or more of mercury and cause respiration to cease. It is in such a state of shock that a cardiovascular or

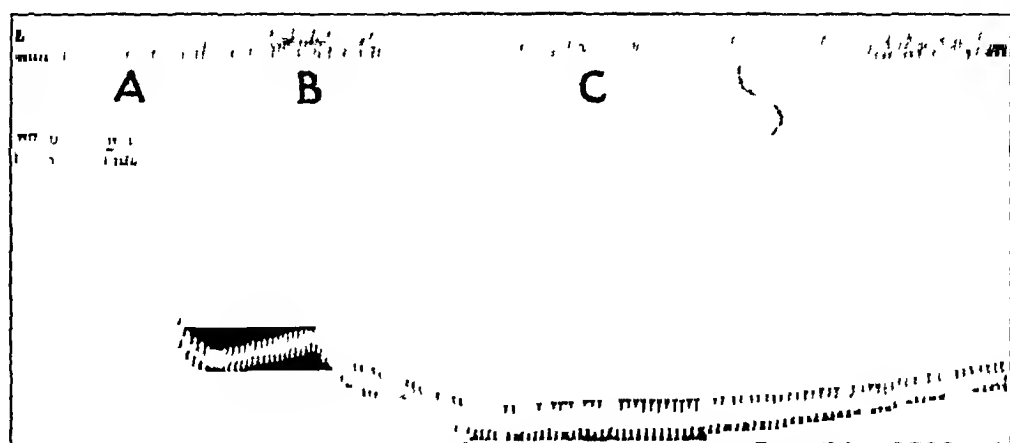


Chart 3—At *A*, 7.5 mg per kilogram of neutral quinidine sulphate was given intravenously. Note the marked customary fall in blood pressure (from 180 to 116 mm of mercury) and slight depression of respiration. At *B*, the same dose of quinidine was repeated with further depression (blood pressure fell to 95 mm of mercury). At *C*, 20 mg per kilogram of cardiazol was given with no appreciable effect on blood pressure or respiration. The slight recovery of blood pressure is less than seen following quinidine without cardiazol.

respiratory stimulant would be of great value. Therefore, in a number of experiments, cardiazol was given while the heart was still beating. Small doses of from 1 to 20 mg per kilogram did not have any effect and larger doses (from 20 to 40 mg) seemed to kill the animal promptly. Although cardiazol did not have a stimulating effect in such marked states of collapse, caffeine alone or with artificial respiration, as observed by Gordon, Matton and Levine,¹⁶ had a prompt and astounding restorative action. This was well illustrated in chart 5; 30 mg of quinidine per kilogram was given (part 1, chart 5), producing a fall of 80 mm in blood pressure and cessation of respiration. Although the blood pressure was greatly reduced, the action of the heart was good, as indicated by the

electrocardiographic record taken simultaneously and by the pulse excursions made on the kymograph. Ten milligrams per kilogram of cardiazol was then given, and a further fall in blood pressure followed with a marked diminution in the pulse. Ten milligrams of caffeine sodio-benzoate was then given, and the pulse rate showed definite improvement, but there was no evidence of return of the respiration, therefore, artificial respiration was instituted at about the rate and rhythm of the normal animal. Respiration quickly returned, the action of the heart improved, and the blood pressure began to rise. A few minutes later (part 2, chart 5), quinidine was given, this time rather slowly so that we might obtain a depressive effect on the respiration without killing the animal. Twenty milligrams per kilogram again caused a fall in the blood

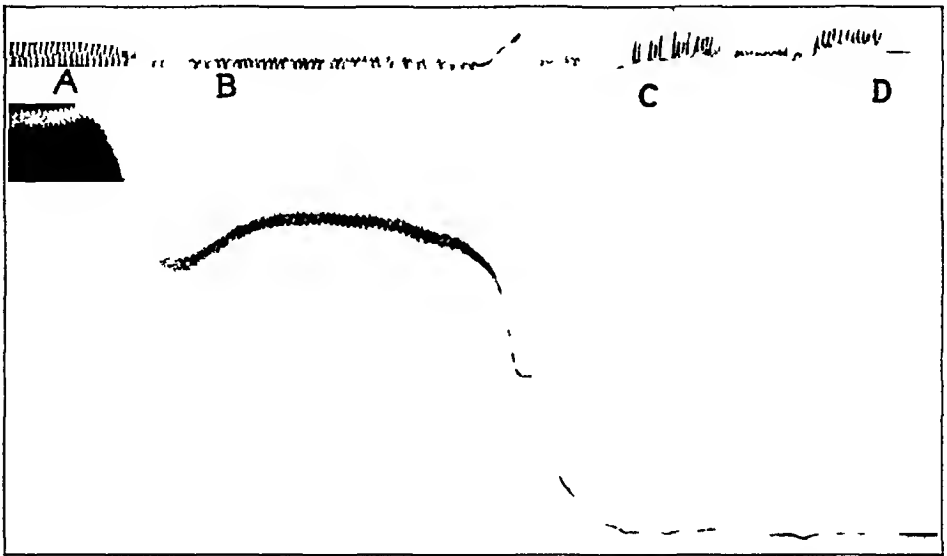


Chart 4—At *A*, 5 mg per kilogram of neutral quinidine sulphate was given intravenously. Note the fall in blood pressure (from 156 to 85 mm mercury), with customary beginning recovery. At *B*, 7 mg per kilogram of cardiazol was given. Note the marked fall of blood pressure with essential arrest of the heart and finally cessation of respiration and death despite artificial respiration between *C* and *D*. This shows that cardiazol aggravated the depressed state.

pressure, a decrease in the pulse amplitude and almost a cessation of the respiration. At this point, 10 mg per kilogram of caffeine was given. A remarkable and prompt return of respiration, heart action and blood pressure followed. The animal recovered, and a better state was present than just before the second dose of quinidine was given, in fact, the cat seemed in almost as good condition as when the experiment was started, therefore the administration of quinidine was repeated (part 3, chart 5). This time the dose was only 10 mg per kilogram, but it was followed by a fall in blood pressure of 15 mm and a moderate decrease in rate and amplitude of respiration. At this point, 10 mg per kilogram of

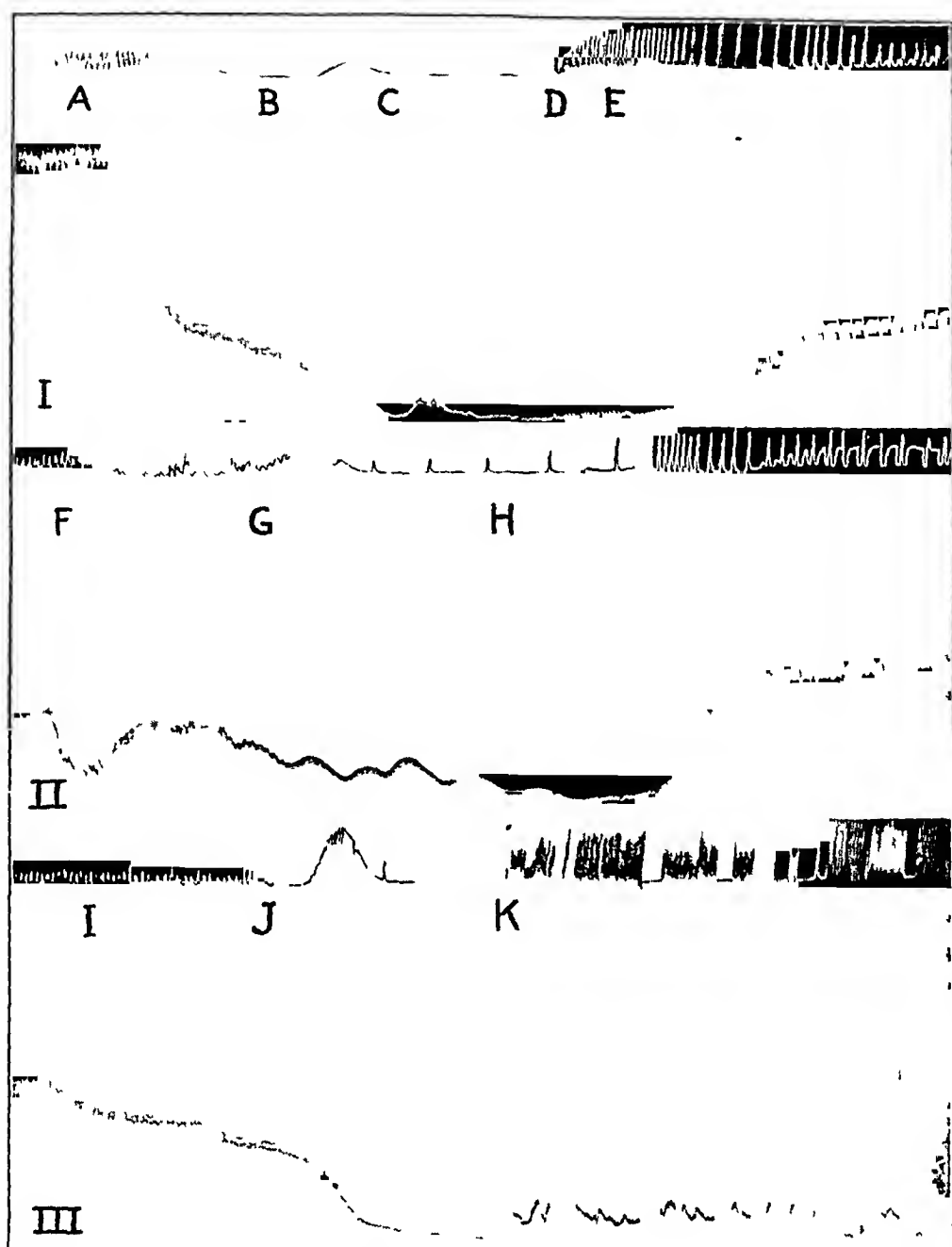


Chart 5—Intervals of about ten minutes lapsed between upper tracing (I) and middle (II) tracing and between middle and lower tracing (III) At A, 30 mg per kilogram of neutral quinidine sulphate was given. Note the marked fall in blood pressure (from 190 to 110 mm of mercury) and cessation of respiration. At B, 10 mg per kilogram of cardiazol was given, followed by a further fall in blood pressure (from 110 to 76) and a decrease in pulse amplitude. At C, 10 mg per kilogram of caffeine sodio-benzoate was given. A slight increase in pulse amplitude resulted, but no effect on respiration. Between D and E, artificial respiration was followed with prompt improvement of circulation and respiration. Between F and G, 20 mg per kilogram of quinidine was given slowly. Respiration almost ceased, pressure fell and pulse amplitude diminished. At H, 10 mg of caffeine sodio-benzoate was given with prompt recovery. At I, 10 mg per kilogram of quinidine sulphate was given with a slight depression and at J, 10 mg per kilogram of cardiazol, which resulted in further depression. The animal died despite artificial respiration and cardiac massage (K to L). This experiment shows that cardiazol failed to improve the depressed state under circumstances in which caffeine restored the circulation, and finally, that cardiazol was fatal when the animal would have otherwise recovered.

cardiazol was followed by the same type of depression as that noted in part 1 of chart 5. Artificial respiration was tried, then both artificial respiration and cardiac massage was carried out for a prolonged time, however, the animal died in much the same manner as in the experiment illustrated in chart 4. Recovery was to have been expected if this final dose of cardiazol had not been given. The foregoing experiments show definitely not only that cardiazol failed to improve animals in artificially depressed states, but that it even aggravated the condition.

Further methods of inducing a state of shock or depression were employed in order to test the value of cardiazol. Experimental hemorrhage was produced by removing varying amounts of blood. From fifteen to fifty cubic centimeters of blood was withdrawn from a vein, causing varying falls in blood pressure (chart 6). Then cardiazol in several different sized doses was given, but improvement was not

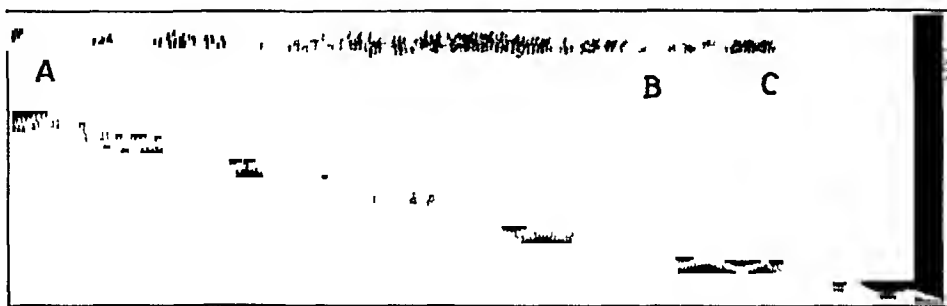


Chart 6—From *A* to *B*, 25 cc of blood was removed from the femoral vein. Blood pressure fell from 190 to 140 mm. At *C*, 25 mg per kilogram of cardiazol was given which produced a slight further depression. The animal slowly recovered. This shows the failure to obtain improvement in the depression produced by hemorrhage.

obtained in four experiments. Likewise, shock was produced by the injection of from 2 to 10 cc of 0.5 per cent solution of sulphuric acid intravenously.¹⁷ In other experiments, acid was given after a brief period of starvation or in conjunction with a slight hemorrhage. Cardiazol did not prove to be of any value in counteracting the depression in any of these experiments.

CONCLUSION

In a series of experiments on cats it was found that cardiazol did not have any beneficial effect on the cardiorespiratory mechanism. This was true in the normal animal and in states of depression, produced by quimidine, hemorrhage and acid intoxication.

THE ELECTROCARDIOGRAM IN DIPHTHERIA *

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Circulatory failure has long been recognized as a frequent cause of death in cases of diphtheria. Investigators differ as to the exact mechanism of this process. Some believe that the fall of blood pressure and the circulatory collapse is a result of a myocardial weakness, while others insist that it is due to primary failure of the vasomotor apparatus, either central or peripheral.

Electrocardiographic studies¹ made during the acute stage of the infection show evidences of myocardial damage in a majority of cases. Changes during the acute period are chiefly those of disturbances in auriculoventricular and intraventricular conduction. It is well known that in the late and convalescent periods, an acute collapse or sudden death may occur, usually after slight exertion. There are no reliable clinical criteria by which such a cardiac involvement may be detected during this stage. With a view of determining whether the string galvanometer may give this evidence, a study was made of a group of patients with diphtheria during the convalescent period. Readings were taken of fifteen patients with severe and moderately severe cases of diphtheria during the period of convalescence, usually in the third or fourth week of illness. In all cases, the local condition of the throat had entirely cleared up and the cultures for diphtheria bacilli were negative. The general symptoms of toxemia had disappeared and practically the only abnormality was a heart beat which readily increased in rate. In seven of the fifteen cases, significant abnormalities were seen in the electrocardiogram. The following is a report of these cases.

REPORT OF CASES

CASE 1 —J. D., a man, aged 35, admitted to the contagious hospital on Sept. 10, 1922, had been ill with a sore throat for three days before admission and had received 20,000 units of diphtheria antitoxin on the fifth day. After seven days in the hospital, he showed paralysis of the soft palate. Examination of the heart on September 15 did not reveal any abnormality. He was discharged on September 21.

*From the Medical Service, Minneapolis General Hospital, and the Department of Medicine, University of Minnesota.

1 Rohmer, P. Electrocardiographische und anatomische Untersuchungen über der Diphtherie-herztod und dessen Beziehungen zum Reizleitungssystem, *Ztschr. f. Exper. Path. u. Therap.* **11** 426, 1912. McCulloch, H. Studies on the Effect of Diphtheria on the Heart, *Am. J. Dis. Child.* **20** 89 (Aug.) 1920. Smith, S. C. Observations on the Heart in Diphtheria, *J. A. M. A.* **77** 765 (Sept. 3) 1921. Marvin, H. M. The Effect of Diphtheria on the Cardiovascular System, *Am. J. Dis. Child.* **29** 433 (April) 1925.

after three negative cultures had been made. On October 10, thirty-three days after the onset of the diphtheria, he was admitted to the neurologic service with the following complaints: loss of voice, difficulty in walking, clumsiness in the use of the hands and the fingers, with tingling sensation and general weakness. The neurologic diagnosis was multiple neuritis following diphtheria. Because of an irregular pulse, electrocardiograms were made and ventricular extra systole,

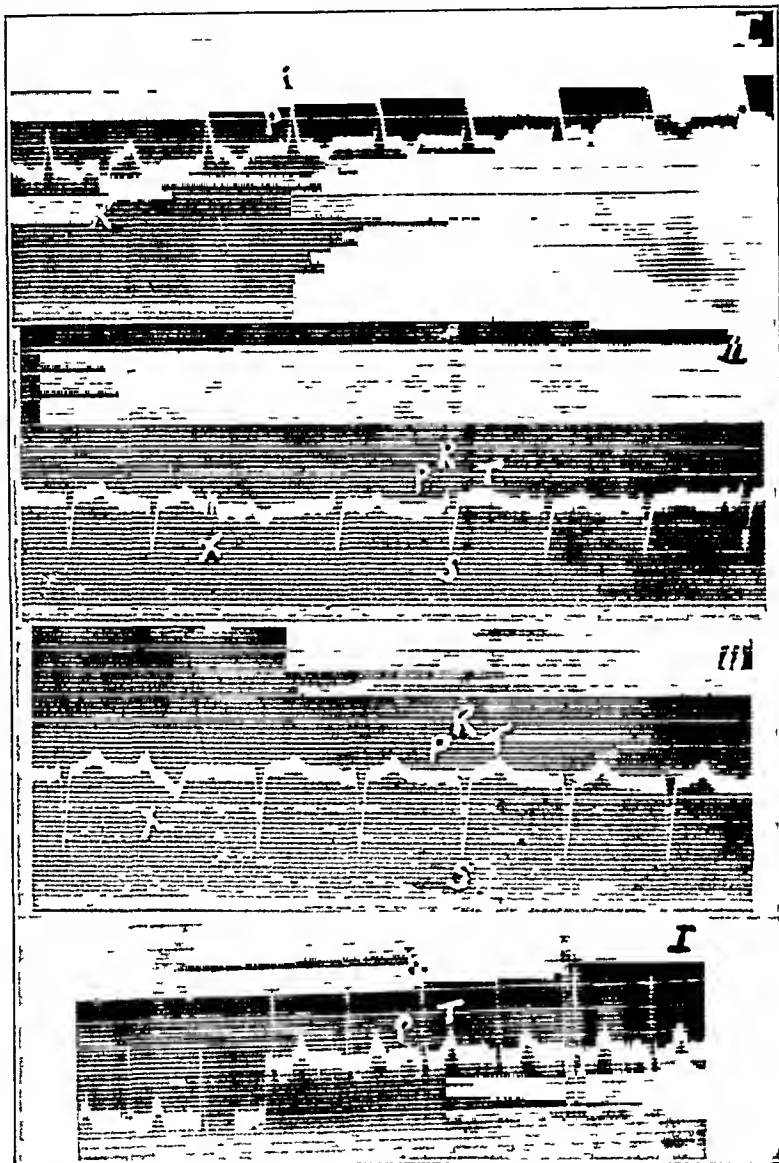


Chart 1 (case 1)—Leads I, II and III, and lead I (lowest record) three months later showing return to an upright T

a left preponderance and an inversion of the T in lead 1 were revealed (chart 1). The patient was kept at rest in bed for three months, and at the end of that time showed a normal upright T in lead 1 (chart 1, lowest record).

CASE 2—M B, a woman, aged 20, entered the contagious hospital on Oct 13, 1925, with a history of sore throat, chills and fever, nausea and vomiting for four days. On examination she appeared toxic, the heart rate was rapid,

the uvula and tonsils were covered by a membrane, and the neck was swollen on both sides, the temperature was 103 F, and the pulse rate, 120. She received 20,000 units of antitoxin. On October 16, the membrane was shrinking and the general condition improved. Her course was satisfactory until October 20, seven days after admission. At 3 15 a m she suddenly complained of pain in the precordium, felt dizzy, vomited and looked pale. A slow pulse varying from 50 to 60 was noted. Stimulants were administered and the patient felt considerably improved during the day. On October 28, cultures of the throat were negative. Her progress had been satisfactory and she was allowed to sit up in bed. Her pulse rate, however, increased on even such slight exertion.

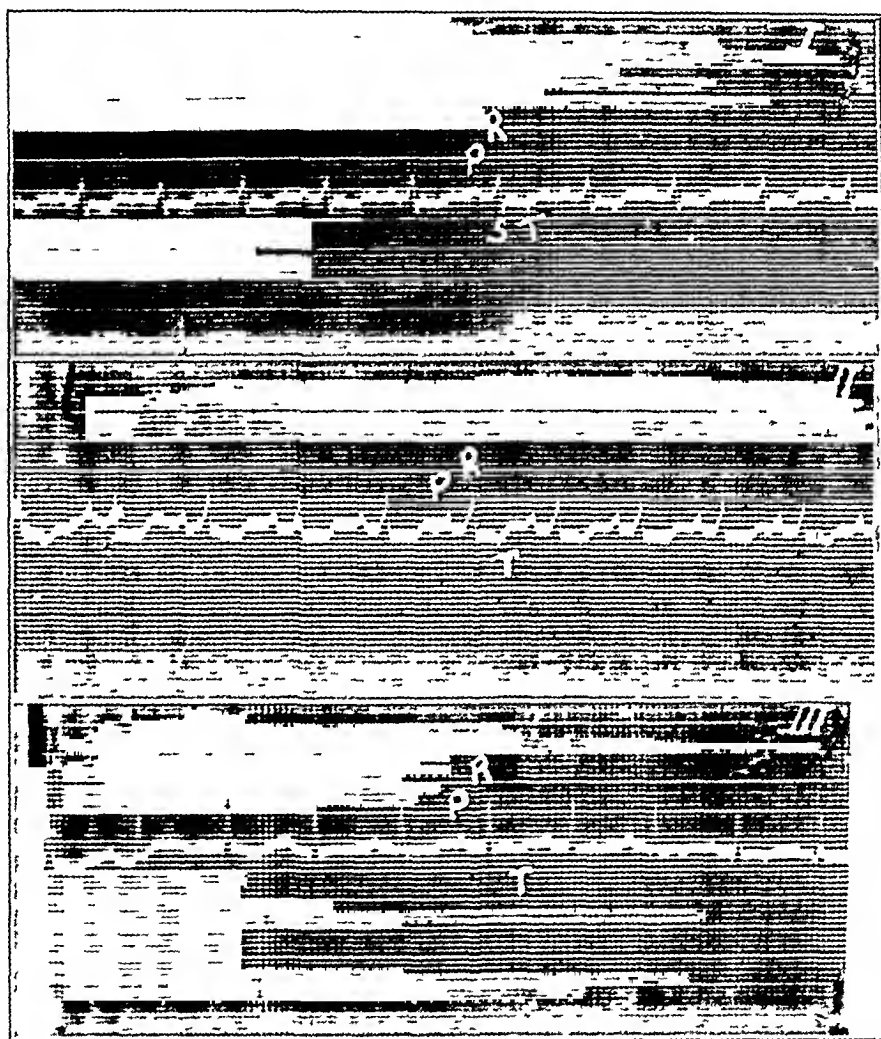


Chart 2 (case 2) —Leads I, II and III showing inverted T in all leads

Physical examination on November 4 revealed a possible slight general dilatation of the heart, a gallop rhythm and an occasional extra systole. The impression was a probable mild degree of toxic myocardium. The following day the heart rate was 102 when the patient was resting and the blood pressure was 110 systolic and 70 diastolic. On November 4, an electrocardiogram was taken (chart 2) which showed inversion of the T in all leads with low voltage. On November 7, another electrocardiogram was taken which was essentially the same as the previous record. On November 11, the patient developed a numbness and peculiar tingling in the right hand and soft palate. On November 13, while sitting up in

bed and reaching for a pitcher of water, she suddenly gasped and fell back. A house doctor saw her at once. Her entire body was rigid, she was breathing in slow gasps, her pulse at the wrist could not be felt and the heart sounds could not be made out. She ceased breathing within a few minutes after the onset. An autopsy was not obtained.

CASE 3—V. H., a school boy, aged 12, entered the pediatric ward on Jan. 7, 1926, because of regurgitation of food through the nose. He gave the following history: On Dec. 3, 1925, he developed a sore throat, and on December 5, anti-

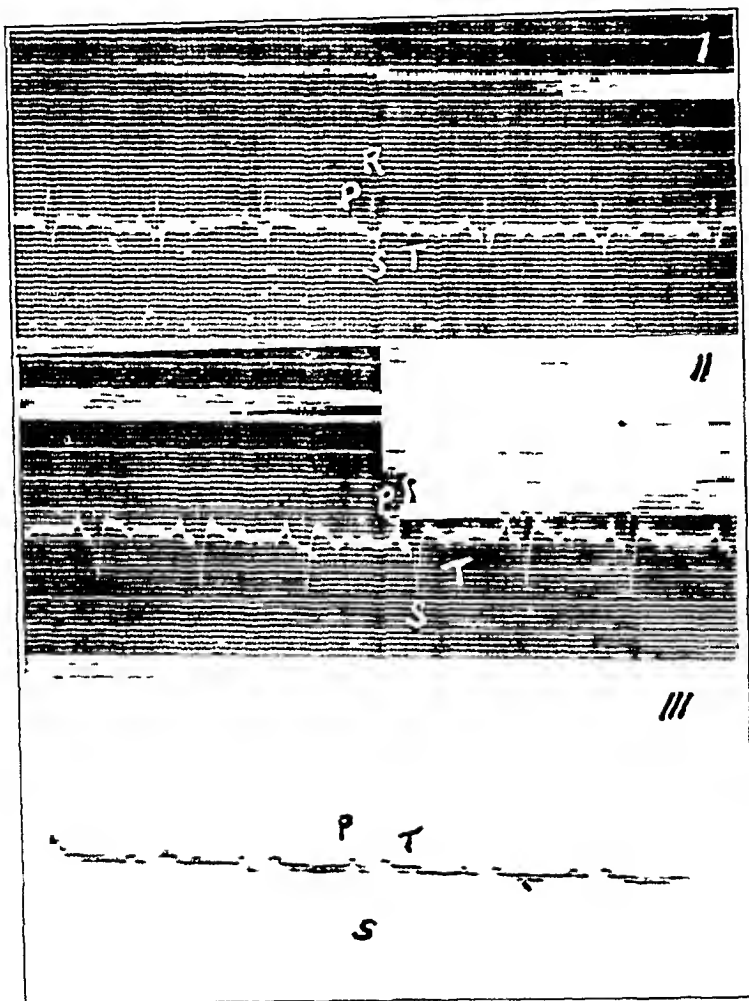


Chart 3 (case 3)—Leads I, II and III showing inversion of T₁ and T₂.

toxin was administered. The infection in the throat cleared up rapidly and he was allowed to be up and around by December 12. He felt weak, however, and tired easily and his mother noticed that his voice was peculiar. It was also noted at this time that there was a regurgitation of liquids through the nose. On examination, his heart was apparently normal with the exception that the rate increased easily on change of position. There was a moderate aphonia and the soft palate did not move on phonation. On January 15, an electrocardiogram (chart 3) showed inversion of the T in leads 1 and 2. The boy was kept in bed and his neurologic signs gradually disappeared. He was discharged on February 1. At this time the T wave was rather low, but had become upright. He returned to

the outpatient department on April 21 feeling well, and at the time an electrocardiographic tracing showed a well developed upright T wave in all leads (chart 4)

CASE 4—L D, a child, aged 6, was admitted to the contagious hospital on Oct 18, 1926, with a history of sore throat for one day, fever and vomiting. A large membrane was present over the tonsils and pharynx and there was a profuse nasal discharge. The temperature was 104 F, the pulse was rapid. The child appeared toxic. Twenty thousand units of antitoxin were administered. The child was seriously ill for ten days, but gradually improved and was discharged with three negative cultures on November 12. At this time an electrocardiogram showed a right preponderance with inversion of the T in leads 2 and 3

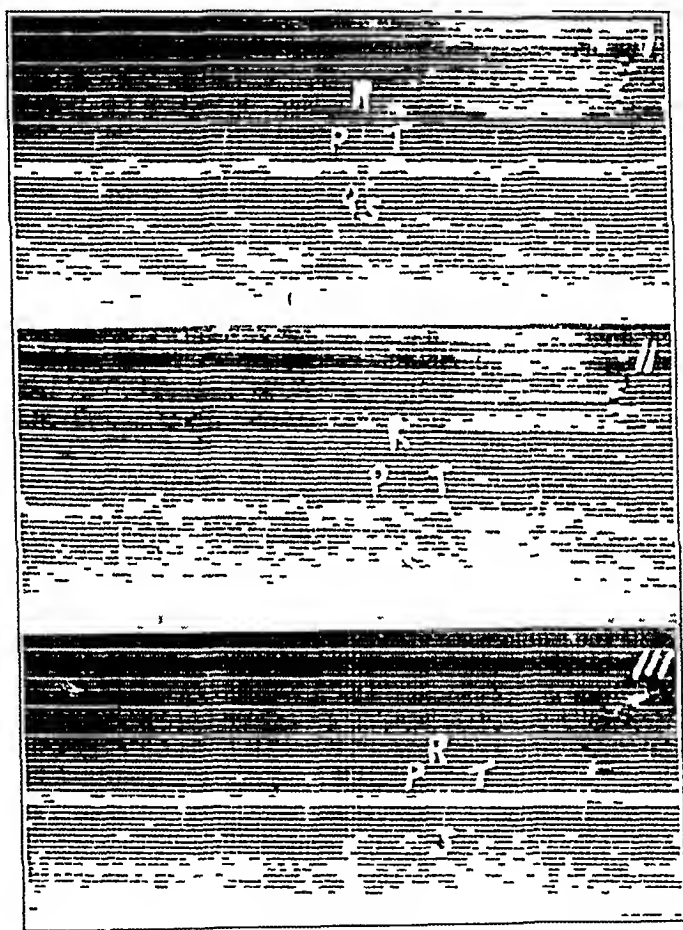


Chart 4 (case 3) —Well-developed, upright T, the electrocardiogram was taken three months after chart 3

(chart 5) The mother was cautioned concerning the child's cardiac condition, and extreme restriction of activities was advised. Another electrocardiogram on Jan 10, 1927, showed normal upright T waves (chart 6)

CASE 5—Mrs M H, aged 42, was admitted to the contagious hospital on Feb 3, 1926, with the history that she had developed a sore throat three days previously, with swelling of the neck and hoarseness. On admission, her temperature was 100.8 F and the pulse rate, 150. Her throat was markedly swollen, and there was marked edema of the soft palate and tonsillar tissues. There was a grayish exudate over the entire pharynx and tonsils, a brawny induration on

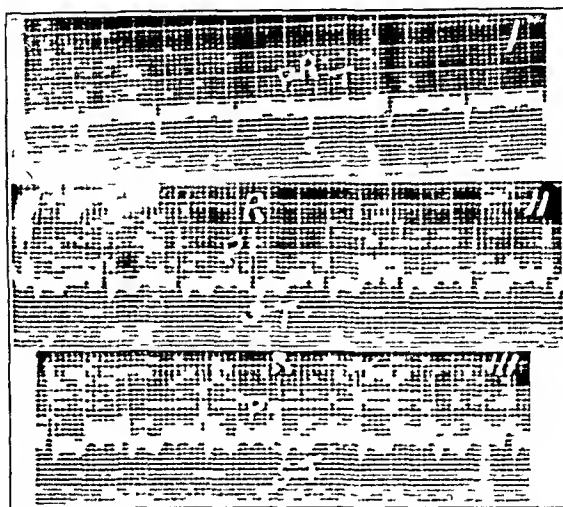


Chart 5 (case 4)—Leads I, II and III showing inversion of T_2 and T_3 in the fourth week

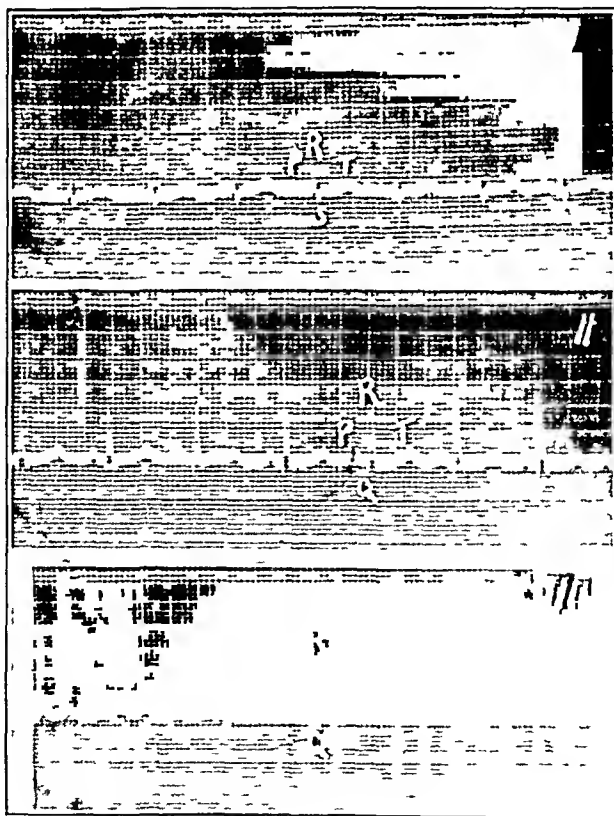


Chart 6 (case 4)—Normal upright T in all leads, taken two months after chart 5

both sides of the neck, the heart tones and chest were normal. The patient was given 20,000 units of antitoxin intravenously. Because of her respiratory difficulty she was intubated. She had great difficulty in retaining the tube, and a tracheotomy was considered. She later coughed up a piece of membrane, and her breathing became easier. On February 15, 10,000 more units of antitoxin were given, the pulse rate was 150, and the patient looked seriously ill. On February 18, the membrane began to disappear and within a week it had entirely cleared up. An elevated temperature was present for about two weeks. On March 6, she developed a tonsillar abscess on the right side and later subcutaneous abscesses developed on the neck. She continued improving, however, and left the hospital on March 17. An electrocardiogram was taken on that day (chart 7) showing inversion of the T-1 and T-2. Three days after discharge from the hos-

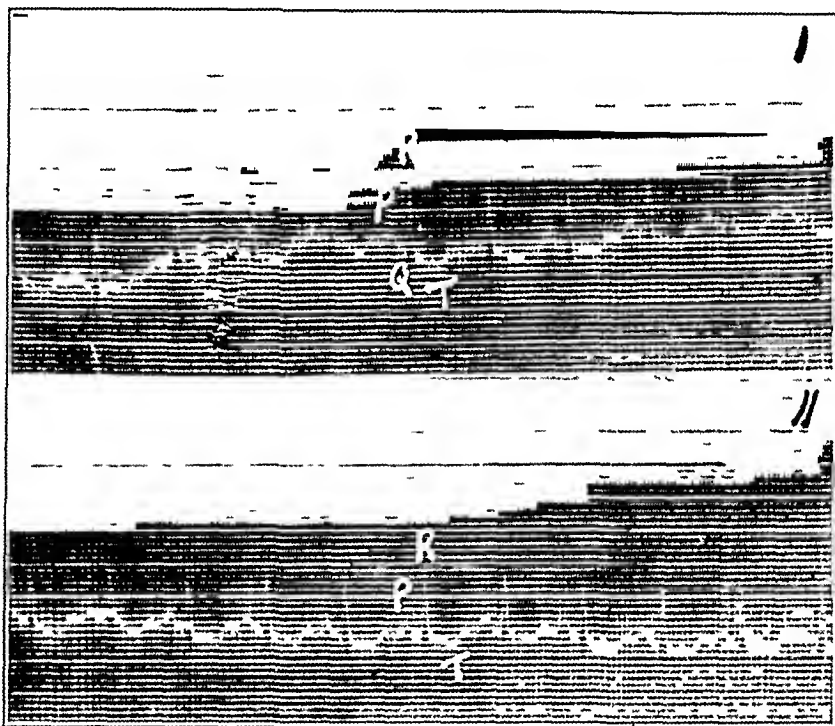


Chart 7 (case 5)—Leads I and II showing inversion of T in the eighth week of the disease

pital, she developed difficulty in swallowing and regurgitation of fluids. Three days later, her difficulty in swallowing became more marked and she died suddenly during the afternoon.

CASE—M W, a woman, aged 24, noticed some soreness of her throat on Nov 14, 1926. Her throat became swollen, and a physician was called who made a diagnosis of diphtheria, and she was admitted to the contagious hospital on November 16. She appeared toxic, with a pulse rate of 90, and temperature, 103 F. Thirty thousand units of antitoxin were administered intramuscularly. The fever was present only three days, and the patient gradually improved. On the eleventh day of her illness, she complained of some precordial pain, and on examination, a mild dilatation of the heart was considered probable. On November 29 an electrocardiogram showed an inverted T in leads 2 and 3 (chart 8). By December 1, she had shown three negative cultures. She showed a marked variation in pulse rate, however, and was transferred to the medical

service on December 9. On examination, her heart seemed slightly out to the left, the rate was 92, but auscultation revealed nothing abnormal. Electrocardiograms were taken several times a week, but did not show any change until Jan 7, 1927, when the inverted T was replaced by an isoelectric T wave (chart 9). On December 22, she complained of some difficulty in swallowing. Some of the food appeared to stick in the upper part of the esophagus. The dysphagia gradually improved, but on January 6, she complained of some numbness in the lower extremities and also tingling in the hands and feet. On January 10, neurologic

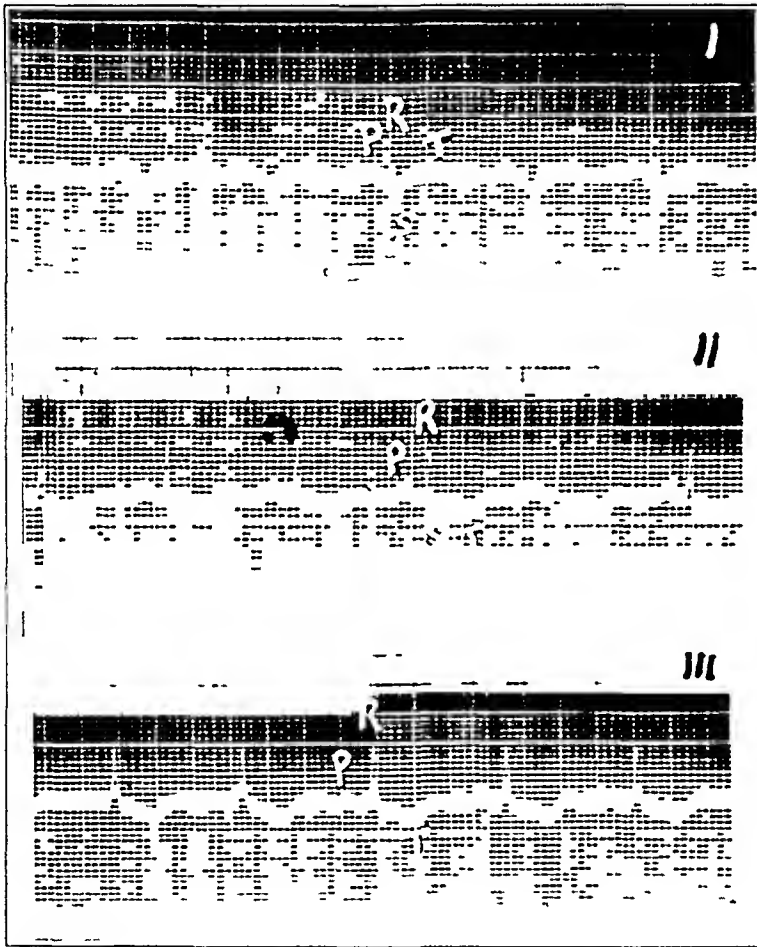


Chart 8 (case 6) —Inversions of T in leads II and III at the end of the second week

examination showed the tendon reflexes present only on reinforcement and muscle power reduced in the lower extremities. The diagnosis was diphtheritic polyneuritis. These symptoms continued for several weeks and gradually cleared up. On January 21, the electrocardiogram showed low but upright T waves (charts 10), in subsequent tracings the T waves became more definitely positive. The patient was again seen on May 26, six and one-half months after the onset. She still complained of some weakness but of no definite symptoms suggestive of cardiac involvement. The physical examination was negative and the vital capacity was normal. An electrocardiogram showed upright T in all leads and the heart was normal in size on roentgen-ray examination.

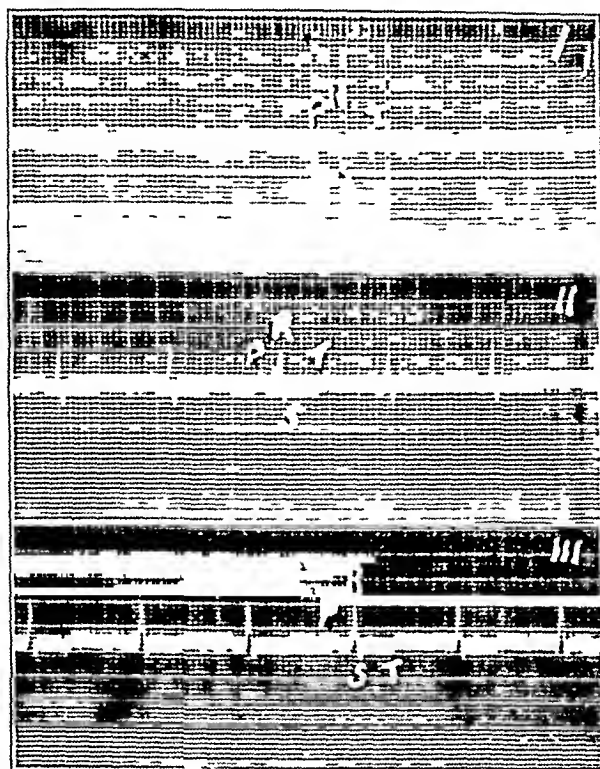


Chart 9 (case 6) —Five weeks after chart 8, showing iso-electric T in lead II

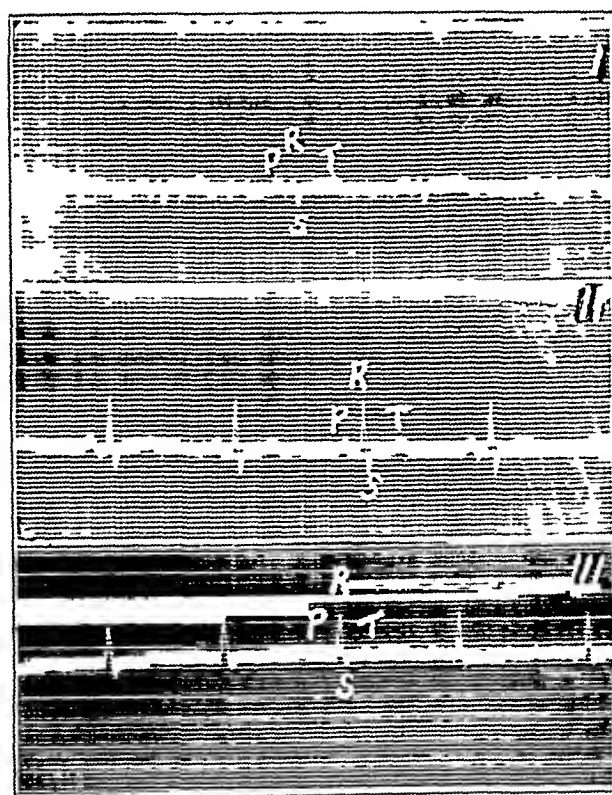


Chart 10 (case 6) —Two weeks after chart 9, showing definite upright T in lead II

CASE 7—C N, a man, aged 19, entered the contagious hospital on Oct 1, 1926. He had complained of a mild sore throat for about a week but had been up and about. Three days before admission, his throat and general condition had become worse, and his neck began to swell on both sides. He was then seen by a physician and sent to the hospital. On admission, he appeared seriously ill, with a temperature of from 102 to 103 F, the pulse rate was 110, and there was considerable difficulty in swallowing. There was a diphtheritic membrane in the throat, a profuse nasal discharge and a marked swelling on both sides of the neck. Thirty thousand units of antitoxin were administered. The patient's condition was serious for about two weeks. He was irrational at times, and apathetic and drowsy at other times. On October 11, he complained of extreme weakness, and became more

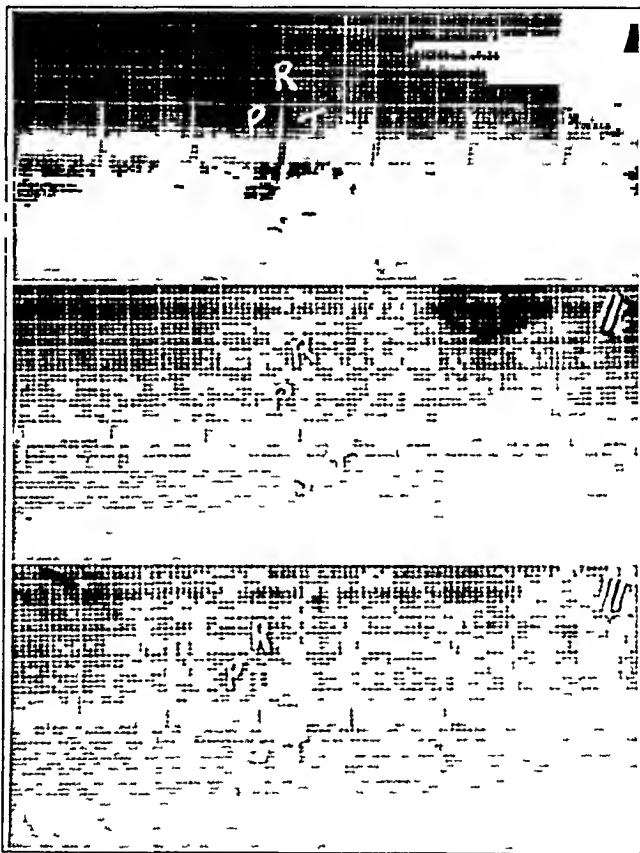


Chart 11 (case 7)—In sixth week of illness, showing inversion of T in leads II and III

stuporous. Respiration was shallow and there was slight cyanosis of the fingers. The pulse rate was 60 and the temperature, 97 F. Two hundred and fifty cubic centimeters of 10 per cent dextrose were administered intravenously. Two days later his pulse rate was still slow, as low as 52. Respiration was shallow, his face was pale, and there was still some cyanosis of the fingers. His circulatory symptoms improved during the day. Following this his general condition gradually improved, but he developed a motoraphasia on October 20, from which he began to recover within two days. During this time he had been running a pulse rate of 60 or below. On October 26, his pulse rate was more rapid, being 72. After four negative cultures were obtained, he was transferred to the medical service on November 4 because of marked lability of the pulse. On examination, the

pulse at rest was found to be 88, the blood pressure was 134 diastolic and 78 systolic. Physical examination of the heart was negative. An electrocardiogram on November 5 showed inversion of T-2 and T-3 (chart 11). Electrocardiograms taken every three or four days did not show any change until November 19, when the T inversion was less marked in degree. On December 3, the T wave was positive but of low amplitude (charts 12). All of the subsequent electrocardiograms were normal.

An analysis of the electrocardiographic observations in these cases shows the following. There was an absence of high grade irregularities,

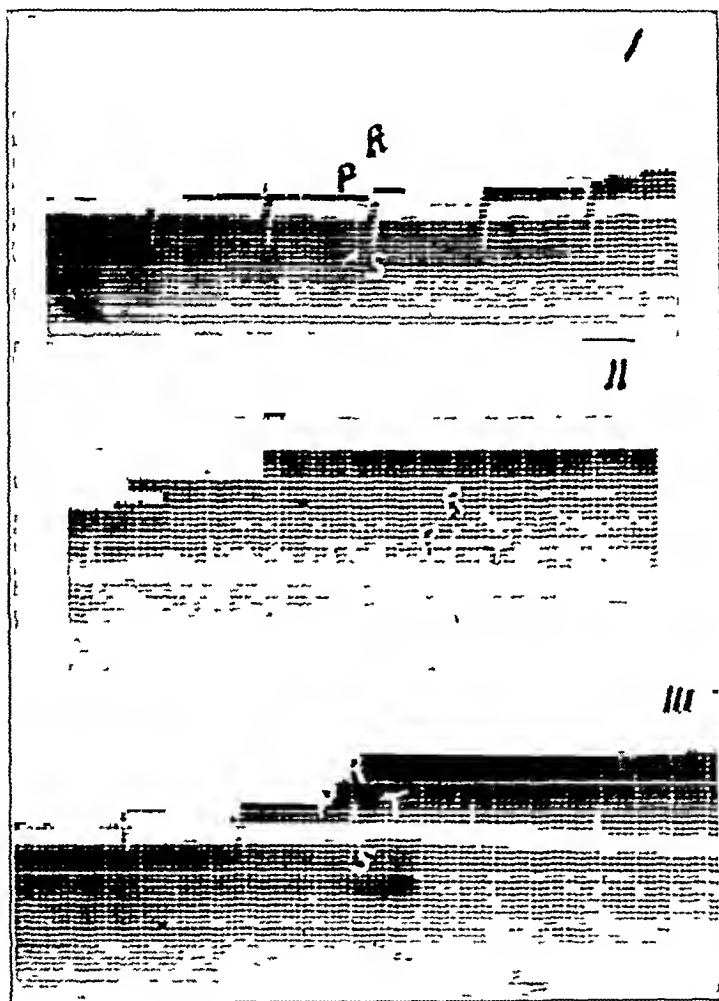


Chart 12 (case 7) —Four weeks after chart 11, showing low but upright T in leads II and III

occasional ventricular extra systoles being the only arrhythmia noted in two cases. There was no evidence of prolonged auriculoventricular or intraventricular conduction time. The longest PR interval was 0.18 seconds and the QRS complex was not altered in any case. The chief significant change was in the T wave. A definite inversion of the T was present in all. In one instance, the T was inverted in lead 1 and in another in leads 1 and 2. In three cases, the change occurred in leads 2 and 3 and in two instances, in all leads. In addition, four

electrocardiograms showed a right preponderance and two a left preponderance. In two cases, sudden death occurred within a week after the readings were taken. The patients have recovered in the remaining five cases, and with recovery the T wave has become upright. The change was a gradual one, the T first becoming less negative, then iso-electric, and later, positive. The earliest evidence of return to normal was noted seven weeks after the onset of the disease. The return of the T wave to normal in the cases of patients who recovered is of interest. It is still believed by some that diphtheria is a cause of cardiac failure in later life. The foregoing observations strongly suggest that the effect is entirely a transient one, and that there is a restoration of normal myocardial function.

THE SIGNIFICANCE OF T WAVE INVERSION

It is generally accepted that the initial portion of the ventricular complex, the QRS, is a composite picture of a spread of the wave of excitation throughout both ventricles. The period between the S and T which usually is at the base line indicates that the entire muscle of the heart is in a state of excitation and therefore there is no difference in electropotential between its various portions. There is still some difference of opinion, however, as to the exact mechanism of the T deflection. The weight of evidence seems to indicate that the T is an electrical expression of the passing off of the excitation wave just as the QRS is a result of the spread of this process. The T wave exists because all portions of the ventricular muscle do not return to the resting electrical state uniformly and synchronously, thereby producing differences in the potential and thus a deflection of the galvanometer string. Normally, the T wave is upright and this is explained on the basis that the apex of the left ventricle returns to its resting state before the base of the right ventricle. It would seem justifiable then to consider an inverted T as an indication of an abnormal retreat of the excitation process in which the apical portions remain in a state of excitation longer than the base.

Experimentally, alterations in the T wave have been produced in various ways, and many of these observations lend support to this conception of the mechanism of the T wave. In frogs, Mines² has demonstrated that on local warming of the apex the T, if inverted will become upright, while if it is positive it will become still more positive. Smith³

² Mines, J. R. On the Functional Analysis by the Action of Electrolytes, *J. Physiol.* **46** 188, 1913.

³ Smith, F. M. Further Observations on the T wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, *Arch. Int. Med.* **25** 673 (June) 1920.

has observed that cooling the apex of the left ventricle of dogs with ethyl chloride spray results in inversion of the T, while the change was of a lesser degree on cooling the middle anterior surface of the left ventricle. Disturbance of the blood supply to the left ventricle by ligating the ramus descendens and circumflex arteries is followed shortly by deep inversion of the T wave. Smith interpreted his results after coronary ligation and cooling of the apex as due to prolongation of the excitation at the apex which has been damaged by these procedures. Hamburger⁴ and his associates have shown that T wave inversion occurs in dogs following experimental embolism from injection of a suspension of *Lycopodium* spores into the coronary circulation.

It is also well known that the introduction of certain substances affect the T wave. In experimental animals and in human beings, digitalis in sufficient dosage will flatten and invert the T wave.⁵ In dogs and cats, ether narcosis may produce a similar effect.⁶ Several observers have studied the effects of nerve stimulation on the form of the ventricular complex. In frogs, Samojloff⁷ found on stimulation of the vagus nerve, inversion of the T wave if it was positive, and if negative it became more strongly so. Dale and Mines⁸ noted that this type of alteration was not constant and at times the T became more markedly positive, while at others, it was entirely unaffected by stimulation of the vagus nerve. When Einthoven⁹ stimulated the vagus nerves of dogs sufficiently to produce marked changes in the P wave and PR interval, he did not find any appreciable variation in the T wave. His observations suggest that in the mammalian heart nerve influences can play a minor part in affecting the T wave.

In the electrocardiogram of human beings, the T wave is found inverted normally with considerable frequency in lead 3. Alterations of the T in leads 1 and 2 are considered of definite significance, however, and there is great doubt whether such a condition ever occurs in the

4 Hamburger, W. W., Priest, W. S., and Bettman, R. B. Experimental Coronary Embolism, *Am J M Sc* **171** 168, 1926.

5 Cohn, A. E., Fraser, F. R., and Jameson, R. A. The Influence of Digitalis on the T Wave of the Human Electrocardiogram, *J Exper Med* **21** 593, 1915.

6 Miller, H. R., Felberbaum, D., and Krigel, H. T. Electrocardiographic Studies of the Effects of Ether upon the Living Cat's Normal Heart, *Am J M Sc* **169** 516, 1925.

7 Samojloff, A. Weitere Beiträge zur Electrophysiologie des Herzens, *Arch f d ges Physiol* **135** 417, 1910.

8 Dale, D., and Mines, G. R. The Influence of Nerve Stimulation on the Electrocardiogram, *J Physiol* **46** 319, 1913.

9 Einthoven, W., and Wieringa, J. H. Ungleichartige Vaguswirkungen auf das Herz, Electrocardiographisch untersucht, *Arch f d ges Physiol* **149** 48, 1912.

normal heart Lewis¹⁰ stated that normally a negative T is never found in leads 1 and 2. In a recent book on electrocardiography, Weber¹¹ said that the inversion of the T wave in the first two leads must always be considered pathologic. Ferguson and O'Connell¹² recently made an electrocardiographic study of 1,812 midshipmen at the Naval Academy. This material consisted of a group of healthy young adults in whom cardiovascular pathologic processes had been excluded by the usual methods. There were no records showing inversion of the T in lead 1. In only eight cases, or less than 0.5 per cent of the total number, a negative, iso-electric or diphasic T-2 associated with a negative T-3 was noted. In view of the fact that only a portion of these cases were true inversions, and that a second record showed a return to normal, this report confirms the general conception that the inversion of T-1 and T-2 is rarely if ever found in the absence of pathologic processes. Furthermore, one is strongly impressed with the almost constant association of the T wave inversion with serious cardiac disease. The pathologic conditions under which T wave changes are most frequently found are the chronic diseases of the myocardium associated with hypertension and coronary artery disease. In the enlarged heart in cases of hypertension, the T wave inversion is usually associated with a left ventricular preponderance. In disease of the coronary arteries, Pardee¹³ and Willius and Brown¹⁴ found T alterations in from 60 to 70 per cent of the cases. In chronic valvular disease, changes in the form of the ventricular complex occur with much less frequency. From extensive statistical studies in all types of cardiac pathologic processes Willius¹⁵ demonstrated the serious prognostic significance associated with inversion of the T wave in the first two leads. Compared with a control group, patients showing this abnormality had a much shorter life expectancy, approximately 60 per cent dying of heart failure within a year. Changes of the T wave in the direction of negativity have been noted with myxedema. Fahr¹⁶ and Thatcher and White¹⁷ described a low and

10 Lewis, T. *Clinical Electrocardiography*, ed. 3, London, Shaw & Company, 1924, p. 36.

11 Weber, A. *Die Elektrokardiographie*, Berlin, Julius Springer, 1926, p. 113.

12 Ferguson, D., and O'Connell, J. T. *Cardio-Vascular Observations*, U. S. Nav. M. Bull. **24** 860, 1926.

13 Pardee, H. E. B. *Heart Disease and Abnormal Electrocardiograms*, Am. J. M. Sc. **169** 270, 1925.

14 Willius, F. A., and Brown, G. E. *Coronary Sclerosis*, Am. J. M. Sc. **168** 165, 1924.

15 Willius, F. A. *Electrocardiography and Prognosis*, Arch. Int. Med. **30** 434 (Oct.) 1922.

16 Fahr, G. *Myxedema Heart*, J. A. M. A. **84** 345 (Jan. 31) 1925.

17 Thatcher, C., and White, P. D. *Electrocardiograms in Myxedema*, Am. J. M. Sc. **171** 61, 1926.

slightly inverted T which increased in amplitude in the positive direction after the administration of thyroid. Wood and White¹⁸ observed T wave inversion in uremia with high nitrogen retention, and they believe that this is due to a toxic effect on the heart muscle. Electrocardiographic studies have also been carried out in some of the infectious diseases. The chief toxic effect observed in these is prolongation of the auriculoventricular conduction, seen most notably in cases of acute rheumatic fever,¹⁹ but also in cases of influenza, pneumonia and

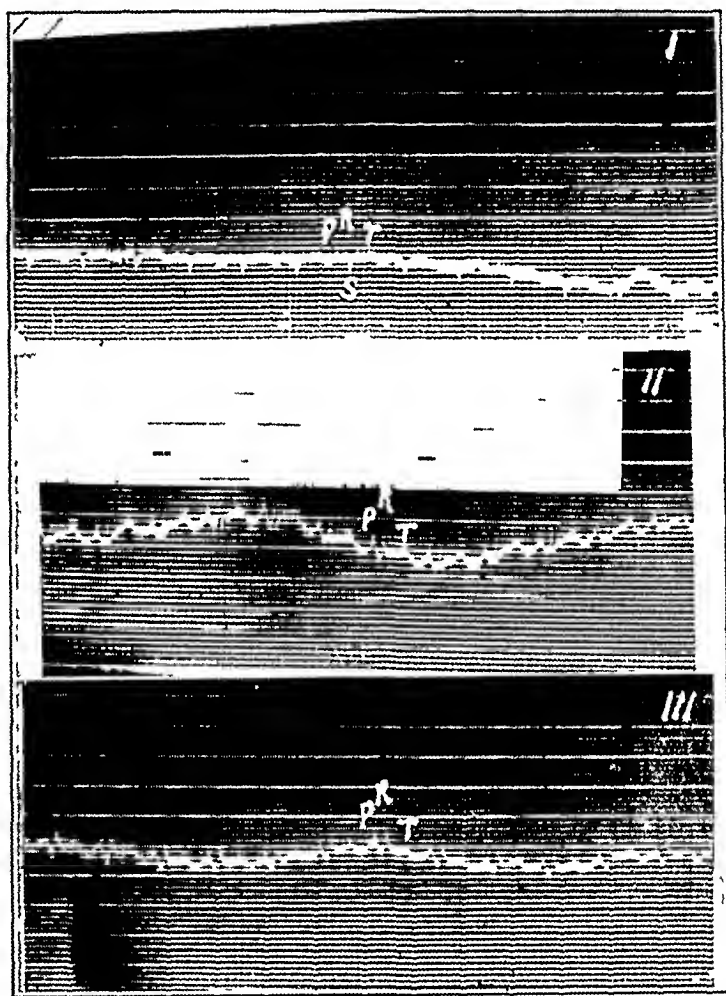


Chart 13—Electrocardiogram of cat 2, before the injection of diphtheria toxin

typhoid fever. Rothschild, Sachs and Libman,²⁰ in a recent report, described an abnormal ST portion of the ventricular complex in rheumatic fever, but no significant changes in the T wave.

18 Wood, J. E., and White, P. D. The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, *Am J M Sc* **169** 76, 1925

19 Cohn, A. E., and Swift, H. F. Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J Exper Med* **39** 1, 1924

20 Rothschild, M. A., Sachs, B., and Libman, E. The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *Am Heart J* **2** 356, 1927

One may conclude from the foregoing physiologic and clinical observations that (1) T wave inversion is probably an expression of an abnormal dying away of the excitation process and may be produced experimentally by injury to the myocardium, especially to the apex of the left ventricle, and that (2) this electrocardiographic abnormality is usually associated with cardiac pathologic processes of a serious nature. The present observations during the period of convalescence in cases of diphtheria suggest strongly that a bacterial toxin may so affect the

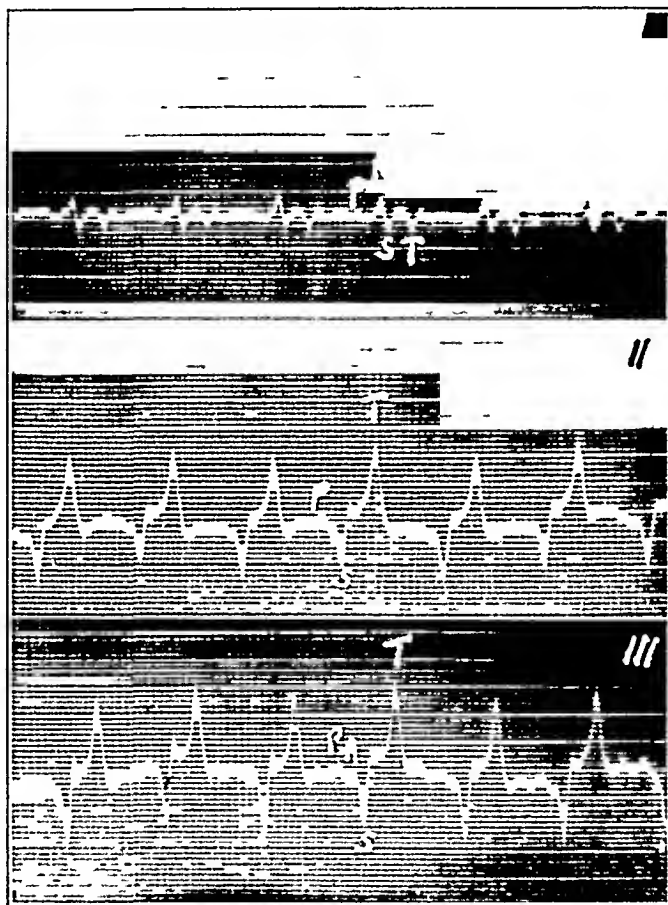


Chart 14—Electrocardiogram of cat 2, showing widening of QRS and inversion of T in lead I, forty-eight hours after injection of diphtheria toxin

passing off of excitation that a negative T wave results. Thus it would seem justifiable to conclude that T wave inversion in addition to its previously accepted significance may also indicate an injury to the heart muscle by a bacterial toxin.

OBSERVATIONS ON EXPERIMENTAL DIPHTHERIA TOXEMIA

An attempt was made further to confirm this by a study of the effects of diphtheria toxin in experimental animals. In the course of an investigation on the problem of whether diphtheria toxin possessed

any special affinity for the conducting tissue of the heart, Rohmer²¹ injected diphtheria toxin into four rabbits. In a brief paragraph, he merely stated that he did not find any evidence of delayed conduction. He did not refer to any other changes. This seems to be the only previous report on the use of the string galvanometer in the study of experimentally produced diphtheria.

Cats were used in the present study, and diphtheria toxin²² was injected subcutaneously. The dose of toxin varied from 0.03 to 0.05 cc

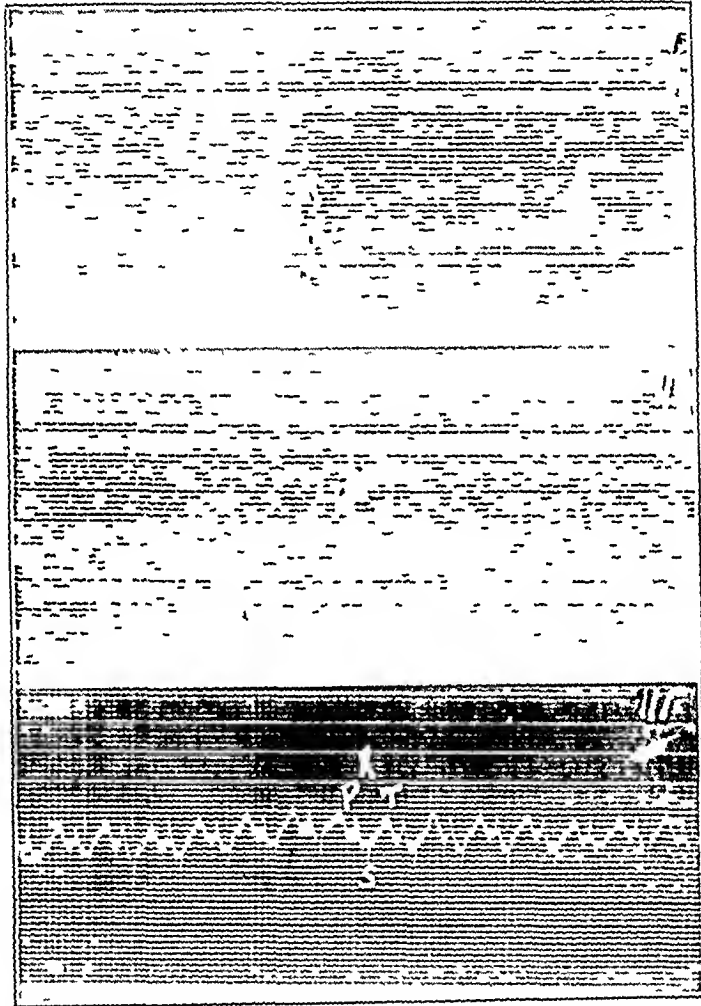


Chart 15—Electrocardiogram of cat 3, before the injection of diphtheria toxin

diluted to 2.5 cc in sterile saline. The records were taken with the animal under light ether anesthesia. After a control record was taken and the toxin injected, subsequent readings were made at forty-eight hours and at varying intervals following this, if the animals remained alive. All the animals exhibited definite evidence of intoxication. The effect was usually noted on the second day following the injection. The

²¹ Rohmer (footnote 1, first reference)

²² The toxin was supplied by Dr. W. P. Larson of the Department of Bacteriology. A minimum lethal dose equals 0.4 cc.

animals became apathetic, moved about little and refused their food. Only a small amount of anesthetic was necessary in taking the subsequent readings as they offered but slight resistance. A frequent observation was weakness and stiffness of the hind legs. This usually occurred on the second or third day.

Of ten satisfactory experiments, electrocardiographic changes were observed in eight after the injection of the toxin. These may be sum-

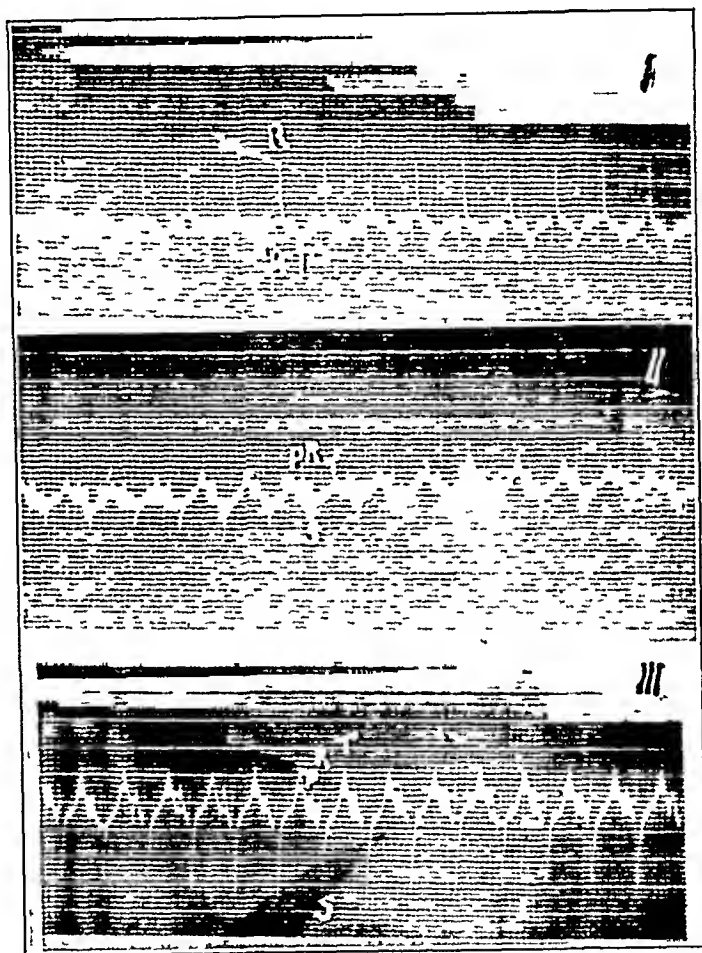


Chart 16—Electrocardiogram of cat 3, forty-eight hours after injection of diphtheria toxin showing inversion of T in lead I and left ventricular preponderance

marized as follows. Definite arrhythmia did not occur. Definite changes in the PR interval and QRS complex were present in but two cases. In one animal, six hours before death, the record showed a PR interval of 0.12 second, where it had previously been 0.06 second. At the same time, the QRS had markedly increased in amplitude and had widened from 0.02 to 0.06 seconds. The tracing was of a type indicating a bundle branch block. In another instance a similar record, but with changes of lesser degree, was noted at forty-eight hours. The most

constant and striking alterations were in the T wave. There was definite flattening and inversion of the T wave in one or more leads in all cases, as early as forty-eight hours following the injection of the toxin. The change was present in lead 1 alone, in three cats, and in leads 1 and 2 in one animal. In the remaining four, the inversion was present in leads 2 and 3. In two cats in whom it was possible to follow results for seven and ten days, a tendency for return of the T to normal appeared between the third and sixth day in one instance, and between

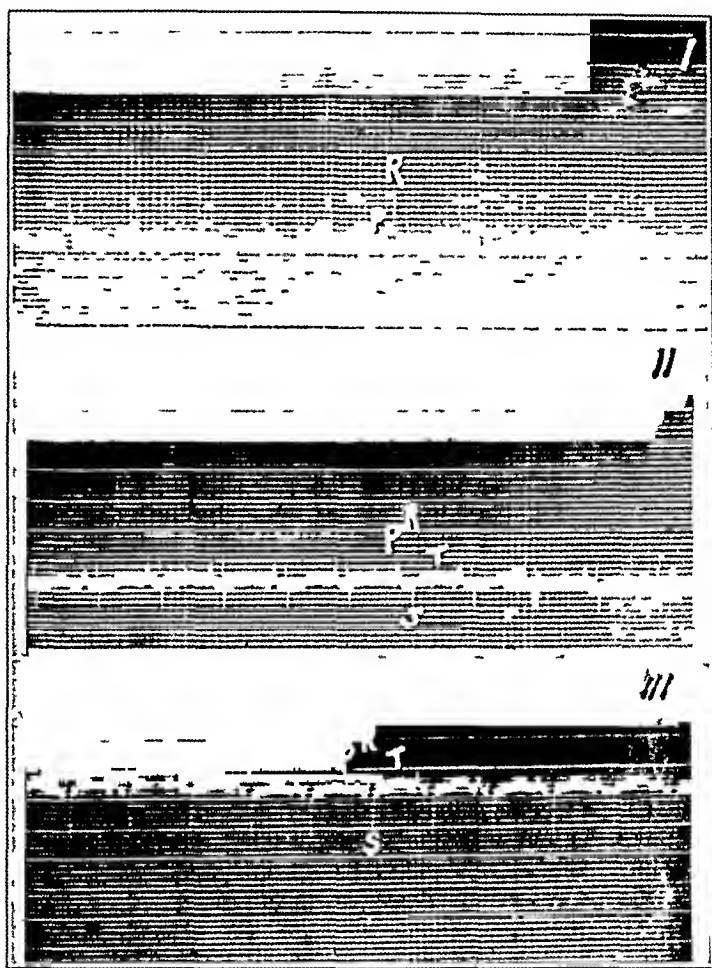


Chart 17—Electrocardiogram of cat 3, showing partial return to normal of T in lead I, four days after chart 16

the fifth and eighth day in the other. In addition, in two animals there was a definite change in ventricular preponderance, both within forty-eight hours, following the injection of toxin. In both cases a definite left ventricular preponderance developed.

Similar rapid changes in preponderance are reported by McCulloch²³ and Marvin²⁴ in their clinical cases. In one case, a definite flaccid paralysis of the hind extremities was present on the tenth day, when the

23 McCulloch (footnote 1, second reference)

24 Marvin (footnote 1, fourth reference)

electrocardiographic changes were returning to normal. This is of interest since clinically diphtheritic paralysis and circulatory failure are often associated, and attempts have been made to explain both on a nervous mechanism. This experiment shows paralysis occurring at a time when there is evidence of recovery in the heart.

COMMENT

Electrocardiographic observations carried out on a series of patients with diphtheria during convalescence, and on cats given diphtheria toxin, show evidence of a definite damage to the myocardium. These observations have some theoretical and practical application. First, they have a bearing on the question of the mechanism of the circulatory failure in diphtheria. Various investigators have noted a progressive drop in blood pressure ending in death after the production of diphtheria toxemia in animals. As already mentioned, there is a difference of opinion as to whether the seat of circulatory insufficiency lies in the heart or in the vasomotor apparatus.

In 1899, Romberg and his associates²⁵ carried out an extensive series of experiments on the circulatory mechanism in infections. Following this it was generally accepted that diphtheria toxin produces a paralysis of the vasomotor center with loss of vasomotor control of the arteries, allowing them to relax so that the circulation fails. The observations of MacCallum,²⁶ using different experimental methods, seemed to confirm Romberg's conclusions. Porter and Pratt,²⁷ on the other hand, concluded that the vasomotor center was unimpaired by diphtheria toxin. Pathologists, pointing out the extensive degenerative changes which may occur in the heart in diphtheria, insist that the myocardial weakness is the essential factor in the circulatory failure. In a recent report, Warthin²⁸ presented an excellent review of the entire subject including a pathologic study of the heart in a group of cases. He concluded that the myocardium shows a characteristic pathologic picture in diphtheria and that the essential lesion is a "toxic parenchymatous hyaline degeneration or necrosis frequently associated with fatty degenerative infiltration and less frequently with cloudy

25 Romberg, E., Passler, H., Bruhns, C., and Muller, W. Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infektionskrankheiten, *Deutsches Arch f klin Med* **64** 652, 1899.

26 MacCallum, W. G. The Mechanism of Circulatory Failure in Diphtheria, *Am J M Sc* **147** 37, 1914.

27 Porter, W. T., and Pratt, J. H. The State of the Vasomotor Centre in Diphtheria Intoxication, *Am J Physiol* **33** 431, 1914.

28 Warthin, A. S. The Myocardial Lesions of Diphtheria, *J Infect Dis* **35** 32, 1924.

swelling or simple necrosis." In a study of nineteen cases Loth²⁹ was unable to demonstrate any specific myocardial lesion and stated that the changes observed were merely cloudy swelling or fat infiltration such as occurs in other acute infections. MacCallum³⁰ does not believe that the structural changes observed impair the function of the heart sufficiently to explain the disturbances in circulation. There are other observers also who maintain that the pathologic conditions in the heart do not offer convincing evidence of the cause of death. One may conclude therefore, that although pathologic studies favor the myocardial theory they do not permit a final conclusion as to the exact part played by the heart muscle. This is not surprising in view of the fact that it is difficult with the present knowledge to correlate disturbances in myocardial function with structural changes in the heart. The electrocardiographic changes noted by Smith,³¹ McCulloch³² and Marvin³³ during the acute stages, and those described in the present report during convalescence, are of a type which is usually found associated with serious cardiac disease in which myocardial function is definitely impaired. It would not be possible to explain these significant electrocardiographic changes by any vasomotor mechanism. These observations therefore offer additional evidence in favor of a myocardial basis for the circulatory failure in diphtheria.

Another of the various theories for the sudden collapse during the period of convalescence in cases of diphtheria is that it is due to a toxic injury of the vagus nerve. This has been suggested because of the well-known fact that diphtheria toxin has a special affinity for nerve tissue, and also for the reason that the circulatory collapse occurs most frequently in cases showing signs of nerve disturbance. It will be noted that six of the seven cases showed some evidence of involvement of the nerves. In most instances, this was mild in character and did not seem to bear any relationship to the extent of myocardial damage. Case 1, for example with evidence of severe injury to the nerve ended with recovery, while case 2 with mild neurologic symptoms, terminated in death. Furthermore in the entire group of fifteen cases there were several in which there was definite paralysis of the soft palate in which the electrocardiograms were normal. It is also of some significance that there was no correspondence in time of onset of the electrocardiographic change and the evidence of nerve disturbance. Case 6, which showed

29 Loth, M. The Heart in Diphtheria. *Arch Int Med* 31:637 (May) 1923.

30 MacCallum W. G. A Text-Book of Pathology, Philadelphia W. B. Saunders Company 1924 p 465

31 Smith (footnote 1 third reference)

32 McCulloch (footnote 1 second reference)

33 Marvin (footnote 1, fourth reference)

inversion of the T on November 29, first gave evidence of return to normal on January 7 with a flat iso-electric T wave, at a time when the neurologic signs were most marked. Similarly case 7 began to show evidence of involvement of the nerve after the T wave had become upright. A similar condition occurred in one of the animals that developed a definite flaccid paralysis of the hind extremities on the tenth day when the electrocardiographic changes were returning to normal. As already mentioned, T inversion has been experimentally produced in some animals by stimulation of the vagus nerve, although Einthoven's observations on dogs indicate that such an effect is extremely unlikely in the human heart. In an attempt to ascertain whether stimulation of the vagus nerve could be playing any part in the T inversion, cases 6 and 7 were studied after the injection of atropine sulphate. This was done at a time when the T wave inversion was definite. Atropine sulphate, 0.002, was injected subcutaneously, and several tracings were taken at intervals of ten minutes following the injection. Although there was marked dryness of the mouth and increased pulse rate, no change was noted in the amplitude of the T. These observations suggest that neither the circulatory disturbance nor the electrocardiographic alterations can be explained on the basis of a nerve injury by diphtheria toxin.

Among those who accept the presence of a myocardial injury in diphtheria there is still a difference of opinion as to the duration of this involvement and its later significance. For example, Schwensen³⁴ considers diphtheria as an important cause of chronic cardiac disease later in life. McCulloch,³⁵ in his conclusions, stated that "myocarditis due to diphtheria has a definite position among the factors that lead to chronic heart failure later in life." On the other hand, Place³⁶ said that he has never found evidence of fibrous myocarditis following diphtheria. The return of the T wave to normal in the cases of this group in which recovery occurred suggested a restoration of the myocardium to a normal state. The indications are, therefore, that the toxic effect is a transient one and that it is improbable that diphtheria is a factor in chronic disease of the myocardium. In case 6, in which examination was made six and one-half months after the onset, the physical condition of the heart and the vital capacity of the lungs, were normal, as was the electrocardiogram, and there was no evidence of dilatation in a roentgenogram of the heart made at a distance of 6 feet

³⁴ Schwensen, C. The Heart Rhythm in Diphtheria, *J. Infect. Dis.* **30** 279, 1922

³⁵ McCulloch (footnote 1, second reference)

³⁶ Place, E. H. *Oxford Medicine*, vol. 5, p. 148

PRACTICAL APPLICATIONS

Although it is generally agreed that involvement of the circulation following diphtheria is of serious import, there is no accurate clinical method for detecting its presence. The late circulatory collapse may come on without warning. The physical examination usually gives no hint of the presence of a serious condition and blood pressure studies do not offer any assistance. Rolleston,³⁷ for instance, stated that blood pressure readings are of little practical value. The present study of the seven patients showing positive electrocardiographic evidence reveals no reliable clinical signs or symptoms by which myocardial involvement may have been suspected. It is true that an irritability of the heart existed, but this is a frequent occurrence in a variety of conditions and is of no value as an indication of myocardial injury. In the physical examination in several instances, there was a transient occurrence of extra systoles and alterations in tone with gallop rhythm. Neither of these is diagnostic of myocardial damage. Some degree of dilatation of the heart is undoubtedly present, and this has been shown by the roentgen-ray studies of Dieteln³⁸ and Dörner.³⁹ The degree of dilatation, however, is such that it would be rather difficult of recognition by the ordinary clinical methods. There was no evidence of gross dilatation in any of the seven cases. Furthermore, when myocardial involvement is suspected, there is no means of knowing the duration of such involvement. This is of considerable importance. From a large experience in contagious diseases, Place³⁶ emphasizes the value of sufficient absolute rest until the evidence of involvement of the heart muscle has disappeared. He stated that in his experience, late death does not occur if the patient is kept at rest for a suitable period. It would seem justifiable, therefore, whenever it is possible to make an electrocardiographic study of the patient with diphtheria during the convalescent period. If inversion of the T wave is found, extreme restriction should be carried out until there is a restoration of the normal upright T wave.

CONCLUSIONS

1 In fifteen severe and moderately severe cases of diphtheria approximately 50 per cent of the patients showed inversion of the T wave in significant leads during convalescence.

2 Two patients showing inversion of the T died suddenly.

37 Rolleston, J. D. *Acute Infectious Diseases*, New York, Phys. & Surg. Book Company, 1925, p. 30.

38 Dieteln, H. *Ueber Herzdilatation bei Diphtherie*, München med. Wchnschr. **52**: 683, 1905.

39 Dörner, J. *Clinical Studies in the Pathology and Treatment of Diphtheria*, Jena, Gustav Fischer, 1918, p. 136.

3 In the patients that recovered, the inverted T wave returned to normal as early as seven weeks after the onset of the disease

4 Cats injected with sublethal doses of diphtheria toxin showed consistently similar T wave alterations, usually within forty-eight hours

5 These observations support the myocardial theory of the circulatory failure in diphtheria

6 Electrocardiographic studies are of practical value in diphtheria during the period of convalescence, to ascertain both the presence of myocardial involvement and its duration

ADDENDUM

Since the writing of this paper, the following case has come under observation

E M, a man, aged 37, was admitted to the General Hospital on Nov 2, 1927, with the following complaints marked weakness, difficulty in swallowing, disturbance in speech, diplopia and numbness over the entire body. About three weeks before admission the patient noticed weakness of his upper and lower extremities accompanied by a feeling of numbness. He also noticed that his vision became blurred. About two weeks before entering the hospital, he was forced to discontinue his work because of inability to walk. At this time he began having difficulty in swallowing so that he choked on eating solid food and liquids frequently regurgitated through the nose. At present he is unable to swallow anything unless he is in the upright position. He is unable to speak clearly, and there is a nasal quality to the voice. He has also noted that in washing his face, he cannot distinguish between warm and cold water.

Physical examination showed marked evidence of polyneuritis. There was inability to converge with the eyes and inconstant diplopia in looking at far objects. The soft palate did not show any response to touch. Liquids regurgitated through the nose. In addition, there was a marked muscular weakness in all the extremities with an absence of tendon reflexes. There was no response to plantar stimulation, and position sense was absent in the extremities. Diagnosis by a neurologic consultant was that of advanced polyneuritis, probably due to diphtheria. On further questioning, the patient gave a history of having suffered a severe sore throat about four weeks previous to the onset of the present symptoms. He had consulted a physician, who had painted his throat daily. His left tonsil was also incised but pus was not obtained. He did not stop his work during the entire period, and was not given antitoxin, as a diagnosis of diphtheria was not made. As myocardial involvement is so frequently associated with diphtheritic neuritis, an electrocardiogram was taken which showed definite inversion of the T wave in lead 1 and a left ventricular preponderance. This was repeated, and showed the same changes. The patient's condition remained about the same until November 11, nine days after admission, when he seemed weaker, became short of breath, and râles were heard in the chest. Two days later, his pulse rate increased to 124, respiration to 42, and he was dyspneic. Five hours later, examination revealed a pulse rate of 142, respiration, 42, and the heart sounds were fetal in character. One hour later, he was found dead in bed.

BASAL METABOLISM

III INFLUENCE OF WORK WITH SPECIAL REFERENCE TO THE THYROID GLAND *

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The rise in metabolism due to work is well known¹ Boothby and Sandiford² found that patients with exophthalmic goiter and adenomatous goiter with hyperthyroidism require nearly twice as much energy for a given piece of work as do normal persons or even patients with other diseases. A comparison of the basal metabolism and the metabolism as influenced by work in a series of fifty subjects is herein reported.

MATERIAL AND TECHNIC

The subjects were of three main groups (a) normal persons (pupil nurses), thirteen, (b) patients clinically considered subjects of exophthalmic goiter or toxic adenoma, fifteen, and (c) other patients, twenty-two.

The basal metabolic rate is determined by indirect calorimetry, measuring the consumption of oxygen. The apparatus is provided with a drum which revolves in eight minutes. During the first five minutes, the technic does not vary from the routine except that explanation is first made of what the subject is asked to do during the last three minutes, and the rope handles to be described lie within his easy grasp, adjusted to his arms' length.

The effect of work is determined during the last three minutes, during which the subject lifts a weight equivalent to one-twelfth the body weight. The load is imposed by placing scales at the foot of the bed, putting on the scales ample weight of indifferent material in a box, balancing the scales, then setting back on the scale bar the "runner" a distance equivalent to one-twelfth the subject's weight. Attached to the weighted box and passing over the foot of the bed are two ropes with handles. At the end of five minutes, the subject is asked to make traction on the ropes just sufficient to maintain the scales in balance with the runner adjusted as described. The results are shown in the table.

Before considering the relation of the basal rate to the work rate, I shall refer to six cases (14, 16, 30, 36, 37 and 40) in which there was incomplete agreement between the basal rate and part of the clinical or pathologic evidence. In case 14, the pathologic report of mild toxicity was not supported by other evidence. In cases 16, 37 and 40, the patients are believed to have shown lower basal rates than they would have done except for previous recent treatment by the roentgen-ray, compound solution of iodine or both. The patient in case 30 had

* From the Medical Service of St. Luke's Hospital.

1 Lusk, G. Science of Nutrition, Philadelphia, 1923, p. 310.

2 Boothby, W. M., and Sandiford, I. Basal Metabolism, *Physiol. Rev.* **4**, 95, 1924.

Data Relating to Subjects Included in the Study

No	Date 1927	Name	Age	Sex	Basal Metabolic Rate	M R with Load	M R with Less Load	B M R	Goniter	Previous Treatment	Chemical Diagnosis	Thyroid Treatment	Pathologic Diagnosis
1	Mar 18	S S	19	F	+10	+22	12	0			Normal		
2, 1	Mar 23	S H	20	F	-6	+22	28	0			Normal		
3	Mar 24	P T	22	F	+8	+22	14	0			Normal		
4	Mar 25	W S	23	F	+16	+32	16	0			Normal		
5	Mar 29	R N	24	F	+12	+24	12	0			Normal		
6, A	Mar 31	W N	23	F	-8	+30	38	0			Normal		
7	April 4	T S	20	F	+8	+20	12	0			Normal		
8	April 4	M N	23	F	+11	+24	10	0			Normal		
9	April 5	T X	24	F	+4	+12	8	0			Normal		
10	April 13	N L	45	M	+38	+62	21	+			Normal		
11	April 14	A D	38	F	+10	+22	12	0		Thyroid extract	Chronic infectious tonsillitis, exophthalmic goiter	Tonsilectomy, roentgen ray	Exophthalmic goiter "mild"
12	April 15	O C	10	M	+12	+100	38	+		Compound solution of iodine	Myxedema	Thyroid extract	Exophthalmic goiter "mild"
13	April 20	J W	13	F	+15	+34	19	0		Thyroid extract	Exophthalmic goiter	Thyroid extract	Exophthalmic goiter "mild"
14*	April 20	H P	16	M	-1	+4	8	+			Hypothyroidism	Thyroid extract	Adenoma cystic, mildly toxic
15	April 20	N H	12	F	-2	+10	12	0			Cystic goiter	Thyroid extract	Adenoma cystic, mildly toxic
16, A*	May 5	D S	29	F	+5	+12	17	+		Skin counts, 6 months before, compound solution of iodine	Ovarian cyst	Thyroidectomy	Toxic adenoma (hemorrhagic)
17	May 7	N V	38	F	+50	+80	24	+			Exophthalmic goiter	Thyroidectomy	Adenoma in exophthalmic goiter
18	May 11	S T	20	M	-25	-6	19	0			Hypothyroidism	Thyroid extract	Exophthalmic goiter
19	May 21	A D	25	F	-10	+10	20	+			Myxedema	Thyroid extract	Exophthalmic goiter
20	May 23	E T	21	F	+56	+78	22	+			Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
21	June 1	M B	26	F	+16	+84	38	+			Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
22	June 8	McC	52	F	+12	+22	10	+			Thyroiditis, acute, chronic infectious tonsillitis		
23 B	June 10	B Y	18	F	+22	+38	6	0		Not basal	Chronic cystitis, chronic infectious tonsillitis	Tonsils removed	

	June 13	G P	30	F	+60	+92	32	+	Compound solution of iodine	Toxic goiter	Thyroidectomy	Exophthalmic goiter
24	June 15	L S	23	F	+16	+18	2	0		Normal		
25	June 15	B R	20	F	+8	+24	16	0		Normal		
26	June 15	C C	48	M	+38	+88	50	+		Exophthalmic goiter chronic infectious tonsillitis	Thyroidectomy, tonsils removed	Adenom ^a , col- loid and exoph- thalmic goiter
27	June 18									Normal		
28	June 23	O S	22	F	-2	+12	14	0		Pregnancy, toxic adenoma	Abortion, thyroid- ectomy	Toxic adenoma
29	June 24	E H	11	F	+64	+88	24	+		Pulmonary tuberculosis, chronic psychosis, nontoxic adenoma	Thyroidectomy	Adenoma
30,B*	Sept 30	M C	33	F	+33	+42	9	+		Exophthalmic goiter	Thyroidectomy	
31	Oct 4	M D	43	F	+42	+70	28	0		Tuberculosis of thyroid	Thyroidectomy	Active exoph- thalmic goiter
32,B	Oct 5	L W	37	F	+22	+40	18	+		Duodenal ulcer, chronic infectious tonsillitis	Thyroidectomy	Tuberculosis of thyroid
33	Oct 5	N W	37	F	-16	+1	17	0		Chronic cholecystitis and appendicitis	Thyroidectomy	
34	Oct 5	P D	50	F	-6	+8	14	0		Tachycardia, chronic infectious tonsillitis		
35,A	Oct 6	N C	50	F	± 0	+24	24	0		Diabetes, nontoxic adenoma		
36,A*	Nov 7	A F	51	F	+20	+48	28	0		Exophthalmic goiter		
37*	Nov 8	J W	40	F	+18	+26	8	+	Roentgen ray, compound solution of iodine	Toxic adenoma Patient's suspicion of goiter	Thyroidectomy	Exophthalmic goiter Adenoma
38	Nov 10	M J	48	F	+19	+32	13	+		Exophthalmic goiter	Thyroidectomy	
39	Nov 12	R G	20	F	-11	+4	15	"Not path,"		Exophthalmic goiter		
40,A*	Nov 11	M M	12	F	+18	+40	22	+	Compound solution of iodine	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
41	Nov 11	R M	17	F	-6	+10	16	"Full"		Myxedema		
42	Nov 16	C P	27	F	-7	+10	17	0		Pyorrhea, nephro- lithiasis	Thyroid extract	
43	Nov 18	P H	67	F	+1	+20	16	0		Cancer of uterus		
44	Nov 18	L H	22	F	+2	+10	8	"Full"		Chronic infectious tonsillitis, antrum and teeth		
45	Nov 21	J K	35	F	-7	+5	12	"Full"		Slight simple goiter		
46	Nov 22	R F	11	F	± 0	+15	15	0	Not basal	Normal		
47	Nov 23	M C	22	F	-14	+1	15	+		Simple goiter		
48	Nov 28	D D	25	F	+32	+74	42	0		Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
49	Nov 28	L H	32	F	+52	+116	64	0		Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
50	Nov 30	L F	60	F	-12	-3	9	0		Permeous anemia		

* In these cases there was incomplete agreement between the basal rate and part of the clinical or pathologic evidence

pulmonary tuberculosis, was an inmate of a psychiatric institution and the single rate determination is not believed to be truly basal. In case 36, the patient had diabetes mellitus and an adenomatous thyroid gland believed to be nontoxic.³

The comparison between the basal rate and the rate induced by the load is best seen in the chart.

In plotting the chart, the basal rate is scaled on the base line and the rise in rate on a vertical line. It is to be noted that the difference between the basal rate and the work rate is plotted and not the percentage of the patient's normal to which the rate rose. The field is arbitrarily divided by heavy lines at plus 20 on the basal rate scale and 20 per

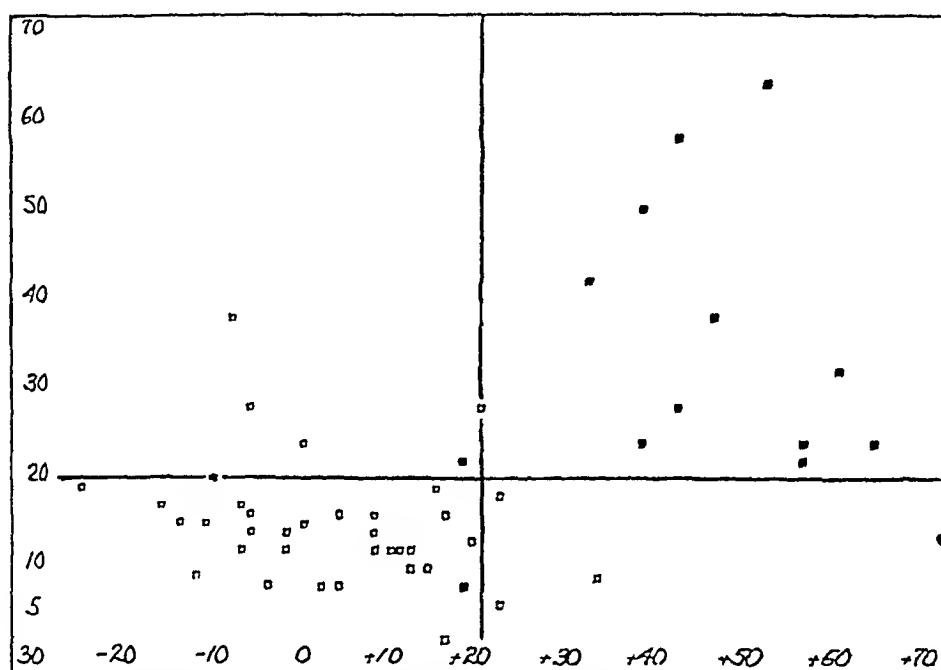


Chart showing comparison between the basal rate and the rate induced by the load. The basal rate is scaled on the base line and the rise in rate on the vertical line. The dark squares indicate results for patients with exophthalmic goiter or toxic adenoma, the light squares indicate results for other subjects.

cent rise on the work scale. Examination of the chart reveals a marked tendency for subjects with a basal rate of less than +20 to show a rise under the load of less than 20 per cent of the subject's normal basal rate, and for those with a basal rate above +20 to show a rise of more than 20 per cent. Of those conforming to the rule, there was only one subject with toxic goiter in the former group (southwest field), and all of the patients had toxic goiter in the latter (northeast field) group. The exceptions may be divided into two groups:

3 As determined by test reported Nov. 29, 1927: basal rate +27, rate with load +42, difference 15, pulse rate 80, 76 and 80 and temperature 99 F.

(a) those showing a basal rate of less than $+20$, but a rise of more than 20 per cent (cases 2, 6, 16, 35, 36 and 40, marked A in the table) and (b) those showing a basal rate of more than $+20$, but a rise of less than 20 per cent (cases 23, 30 and 32, marked B in the table)

Cases 16, 36 and 40 have been discussed. The patient in case 2, a "healthy" pupil nurse, had had diphtheria a year previous to the present illness, the throat had been troublesome since, and tonsillectomy was performed eight weeks after date of the test. In the patient in case 6, a "healthy" pupil nurse, active pulmonary tuberculosis was recognized six months after the test. The patient in case 35 had undergone the prolonged illness and death of her husband, a physician, and failure of economic efforts as keeper of a boarding-house, and had tachycardia and chronically infected tonsils.

Case 30 has been discussed. The patient in case 23 was selected as a nonbasal subject. The patient in case 32 had tuberculosis of the thyroid gland with many giant cells and an absence of typical thyroid hyperplasia.

The various modifying circumstances are not accorded great weight, since it is realized that their exact importance is unknown. They are mentioned, rather, as tending to justify the positive and negative conclusions regarding toxicity of the thyroid gland as shown in the chart.

COMMENT

It is not likely that determination of the basal rate as modified by work will find any wide usefulness as a diagnostic criterion. The limited data presented do not suggest that an abnormal rise due to work over a normal basal rate is specifically related to hyperfunction of the thyroid gland. Further investigation may establish the following tendencies:

A normal or borderline ($+15$ to $+25$) rate rising abnormally under work may, in the individual subject, indicate that the thyroid gland pathologically is toxic, the rate being temporarily depressed under the influence of treatment.

A high basal rate not rising in the degree usually associated with toxic goiter may indicate that the increased basal rate is not due to a pathologic thyroid gland or is not truly basal.

Aside from the influence of previous treatment, the series contains several borderline basal rates with a normal rise (cases 4, 8, 13, 23 and 25), but none of the cases was concluded to be toxic goiter, though the thyroid was diseased in two cases (38 and 32).

The subjects with subnormal basal rates appeared to respond to work with a rise as great or greater than those with basal rates between -10 and $+15$. This agrees with the observations of Boothby and Sandiford.

In this series, the extranormal cost of work of subjects with toxic goiter does not bear a constant ratio to their basal metabolic rate further than that it may be said the cost of work is higher than normal

The average rise of rate in subjects with toxic goiter with basal rates above +20 (12 cases) was 36.9 per cent, varying between 22 and 64 per cent

The average rise in all others, including patients with toxic goiter with basal rates depressed by previous treatment (38 cases), was 14.1 per cent

SUMMARY

In fifty subjects the basal metabolic rate was determined followed by a determination of the rate as influenced by imposing a load of one-twelfth the subject's body weight. All subjects with toxic goiter and with abnormally high basal rates (twelve) showed an increase in rate under the load varying from 22 to 64 per cent of the subject's normal basal rate, and averaging 36.9 per cent. The average of thirty-eight other cases was 14.1 per cent.

Two of the three subjects with toxic goiter and with basal rates under plus 20 who were taking compound solution of iodine showed a rise under the load suggestive of the thyroid hyperfunctional state, one did not show any rise above the normal of 20 per cent.

In three cases in which the basal rates were above plus 20 and in which there was no rise above 20 per cent, none of the patients was found to have toxic goiter.

Of the subjects with borderline basal rates not showing a rise of more than 20 per cent, only the two patients taking compound solution of iodine were found to have toxic goiter.

No ratio appeared to exist between the increased basal rate of subjects with toxic thyroid and their abnormal response to work further than that the cost of work is higher than normal.

An increased response to work did not appear to be a specific thyroid toxic phenomenon.

CONCLUSION

Conclusions cannot be drawn from the limited data, but it is suggested that further investigation, possibly with improved technic may demonstrate that the measured cost of work may be of aid in the diagnosis of toxic thyroid states in a limited number of cases in which the other data are confusing.

My thanks are due Miss Katie Gilliam, technician, for painstaking work in the rate determinations.

TOLERANCE FOR QUININE IN EXOPHTHALMIC GOITER

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About a decade ago, I began making observations on patients with exophthalmic goiter to determine their degree of tolerance to the ingestion of quinine. Part of the deductions derived were published in the nature of a description of the quinine test¹ for patients with exophthalmic goiter. Up to December, 1927, tolerance for quinine was studied in 500 patients. Following my preliminary reports, others made similar observations. Among those, Sainton and Schulman² arrived at negative conclusions, but their data were based on only ten cases. Pfahler,³ on the other hand, found the quinine test extremely useful.

THE QUININE TEST AND RESULTS OF USE OF THIS DRUG

The technic of the test consists in giving the patient a dozen capsules each containing 10 grains (0.65 Gm) of quinine hydrobromide or quinine sulphate, with instructions to take a capsule four times a day. When 20 or 30 grains (1.3 or 1.9 Gm) have been taken by persons in whom the thyroid function is normal or deficient, symptoms of cinchonism develop. A sense of fulness in the head, impaired hearing with tinnitus, occasional dizziness and headache and less frequently gastric and bladder discomfort are experienced. If, however, the person is suffering with exophthalmic goiter,⁴ the daily administration of 30 grains of quinine may be continued with impunity for months, and often distinct improvement is seen in the clinical picture.

The advantages of the quinine test in exophthalmic goiter are its simplicity, its harmlessness and its dependability. The frequency of error is 4.4 per cent in the experiences derived from this series.

Unusual Tolerance to Quinine—In the 95.6 per cent of patients in whom the quinine test was positive, there was unusual tolerance to the

1 Bram, I. Quinine Test, M Rec 98 887, 1920, Quinine Test, Second Report, New York M J 118 339, 1923.

2 Sainton, P, and Schulman, E. Value of Bram Quinine Test in the Diagnosis of Exophthalmic Goiter (Sur la valeur du test de Bram a la quinine comme moyen de diagnostic du goître exophthalmique), Bull et mem Soc med d hôp de Paris 45 1304, 1921.

3 Pfahler, G E. The Treatment of Hyperthyroidism by Radiation, M Clin N Amer 5 854, 1921.

4 The quinine test was found useful in the confirmation of hyperthyroidism with adenomatous goiter, but the percentage of error was somewhat greater than it was in cases of exophthalmic goiter.

ingestion of quinine The table indicates the degree of insusceptibility to cinchonism in the series of patients observed It will be noted that in some cases doses as high as 30 grains were taken three times a day for weeks, without untoward effects In at least 60 per cent of these patients in whom the reaction to quinine was positive material amelioration of symptoms was observed Men seemed able to take larger doses than women Within two or three weeks an increase in weight occurred in many patients, a lessening of excitability and tremor, reduction in thyroid swelling and exophthalmos, marked lowering of the heart rate and a considerable reduction in the basal metabolic rate

Quinine in Treatment—In many patients the therapeutic effect of quinine seems to resemble the remission-producing results of the administration of iodine, with this clinical difference Iodine cannot be given for more than two or three weeks without danger of aggravating the

Tolerance for Quinine in 500 Cases of Exophthalmic Goiter

Quinine-Negative	
Patients intolerant to quinine	6 (1.2%)
Patients tolerating 15 grains (0.9 Gm.) daily	16 (3.2%)
Quinine-Positive	
Patients tolerating 30 grains (1.9 Gm.) daily	158 (31.6%)
Patients tolerating 40 grains (2.6 Gm.) daily	104 (20.8%)
Patients tolerating 60 grains (3.9 Gm.) daily	94 (18.8%)
Patients tolerating 80 grains (5.2 Gm.) daily	68 (13.6%)
Patients tolerating 90 grains (5.8 Gm.) daily	54 (10.8%)
Total	500

symptoms of exophthalmic goiter Moreover, iodine always increases the thyroid swelling by increasing the colloid content of the organ Quinine can be given for months, without harm, to patients in whom the test is positive, and its effect on the thyroid gland is that of marked reduction in size

It must not be construed, however, that quinine, whatever its virtues, is the main factor in the treatment of patients with exophthalmic goiter A mere drug cannot be depended on for the cure of this disease Quinine, however, the basis of the Forchheimer treatment, may be regarded as a valuable constituent in the armamentarium of the experienced internist who has sufficient confidence in himself to treat successfully patients with exophthalmic goiter without resorting to an operation

Intolerance for Quinine—In six patients marked idiosyncrasy to quinine was observed In four, this was heralded by erythematous areas on the skin with subdermal swellings, which soon developed into

definite dermatitis with extreme itching and a moderate rise in temperature. Within a week or ten days desquamation closely resembling that occurring during convalescence from scarlet fever took place. The readministration of as small a dose as 1 or 2 grains (0.06 or 0.1 Gm.) daily for a day or two resulted in the prompt reappearance of untoward effects.

Relative Intolerance for Quinine as an Index to Recovery.—When the basal metabolic rate has become normal and all the signs and symptoms of the disease have disappeared the patient formerly capable of taking from 30 to 90 grains (1.9 to 5.8 Gm.) of quinine daily complains of a sense of fulness and roaring in the head, some deafness and at times dizziness. The reduction of the dosage even to 15 grains (0.9 Gm.) a day may still elicit evidences of cinchonism. An occasional patient may appear well and still possess a relative immunity to cinchonism; in such instances there appears to be susceptibility to relapse indicating the need for further treatment. When however a patient formerly not susceptible to cinchonism almost abruptly begins to complain of tinnitus and allied symptoms and when this cannot be traced to other causes studies on the basal metabolism will indicate that recovery is at hand, and that the patient is ready to resume his or her customary activities.

CONCLUSIONS

1. In 95.6 per cent of patients with exophthalmic goiter a relative immunity to cinchonism exists, large doses of quinine may be taken with impunity and even with benefit.

2. This is the basis of the quinine diagnostic test for exophthalmic goiter which is submitted as an asset in the differentiation of this disease from such conditions as effort syndrome, early tuberculosis, neurasthenia and other conditions commonly confused with exophthalmic goiter.

3. In the form of the hydrobromide or the sulphate quinine is a valuable constituent of the therapeutic armamentarium of the internist who treats patients with exophthalmic goiter and should be given in the average case in much larger doses than has been the custom.

EXPERIMENTAL HYPOTENSION IN RABBITS *

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AND

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The prevalence of lowered blood pressure in chronic infections caused us to feel that some of the micro-organisms present in such infections might have properties which lower the blood pressure. The experiments reported were undertaken with this possibility in mind.

MATERIAL AND METHOD

Rabbits were used exclusively in the experiments. Systolic blood pressures were determined in the central artery of the ear according to the method described by Anderson¹. With his apparatus, the obliteration of the central artery was observed through a rubber membrane. With our apparatus, the rabbit's ear rested on a rubber diaphragm covering a pressure cup and a glass plate was adjusted over the ear so that it just cleared the surface without exerting pressure. Thus observations were made through glass instead of through a rubber diaphragm. A detailed description of the apparatus is given elsewhere.² The mean of a series of five consecutive readings was recorded as the pressure, and with rare exceptions the variation of separate readings was not over a few millimeters of mercury. Care was taken at all times to prevent fright or excitement in the animal, and approximately the same portion of the central artery was used for all readings.

After preliminary observations of the blood pressure, rabbits were inoculated with twenty-four hour dextrose brain broth cultures of the composite bacterial flora from the apex of a tooth, a tonsil or prostatic secretion. Teeth were extracted with precautions to avoid contamination, the apices snipped into sterile Locke's solution and shaken with sand as described by Haden³. Material was squeezed from tonsils with a sterile throat mirror. After thorough cleansing of the parts, prostatic fluid was expressed into a sterile Petri dish. Deep tubes of dextrose brain broth were used for cultures in accordance with Rosenow's technique⁴. Rabbits were usually inoculated in groups; one or more were given intravenously 2.5 cc of a twenty-four hour culture per kilogram of body weight, while the others were inoculated in each knee joint with 0.5 cc of the same culture. Two rabbits of the series were inoculated in the medullary cavity of the tibia. The tibia was exposed under urethane anesthesia, a hole drilled

* From the Department of Preventive Medicine, A. O. Smith Corporation.

1 Anderson, H. C. Demonstration of an Instrument for Taking Repeated Blood Pressures in Rabbits, with Report of Some Experiments, *Proc Soc Exper Biol & Med* **20** 295 (Feb) 1923.

2 Squier, Theodore L. Simple Apparatus for Repeated Blood Pressure Determinations in Rabbits, *J Lab & Clin Med* **13** 279 (Dec) 1927.

3 Haden, Russell L. Elective Localization in the Eye of Bacteria from Infected Teeth, *Arch Int Med* **32** 828 (Dec) 1923.

4 Rosenow, E. C. Studies on Elective Localization, Focal Infection with Special Reference to Oral Sepsis, *J Dent Research* **1** 205 (Sept) 1919.

through the cortex with a dental drill and a small pledget of cotton which was saturated with a twenty-four hour culture inserted into the bone marrow cavity. The opening was then plugged with a sterile wooden plug, and the incision was sutured. It was felt that the inoculations into the knee joint and bone marrow would simulate the conditions present in chronic infections.

TABLE 1—*Results of Inoculation with Cultures from Persons with Low Blood Pressure**

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 89 Mm	Pressure Readings Under 101 Mm	Pressure Readings After Inoculation
471A	94	34	K J	51	9	47.6	10	6	7	7
		35	B M	51	11	57.6	14	6	7	8
642A	106	33	I V	113	18	57.2	10	6	10	14
		54	I V	2	18	62.1	14	6	9	14
		65	K J	64	7	56.7	12	4	4	6
12T	104	55	I V	1	20	58.0	12	4	8	15
		67	K J	97	2*	64.8	53	0	0	1
167T	104	109	I V	21	3*	66.5	20	1	1	2
		110	K J	21	10*	62.5	11	5	6	8
979A	96	152	K J	23	169	64.9	8	17	18	63
		153	K J	23	80	63.0	10	25	29	41
		58	I V	23	3*	67.8	43	0	0	2
1070A	106	177	K J	27	67	63.3	16	8	8	29
		178	K J	27	65	61.6	23	5	7	25
		179	I V	27	10*	62.6	40	0	2	4
729T	102	204	I V	1	62	67.0	41	0	0	31
		205	K J	1	32*	65.0	28	3	7	19
		206	K J	1	36*	62.4	10	9	14	28
729A	102	219	K J	3	53	62.4	47	0	0	22
		220	K J	3	54	64.8	42	0	0	22
		221	I V	3	41	63.8	19	4	10	21
729AS	102	210	K J	43	52	62.1	49	0	0	23
		211	I V	43	54	63.4	51	0	0	21
		212	K J	43	52	62.7	43	0	0	22
246A	104	362	K J	2	26	62.1	44	0	0	15
		363	I V	2	27	57.8	29	2	11	15
		364	K J	2	27	57.6	36	0	3	15
1091T	88	227	I V	13	28	65.4	55	0	0	14
		228	K J	13	28	62.0	45	0	0	14
		229	K J	13	28	60.8	43	0	0	14
1042P	102	154	I V	22	75	65.0	42	0	0	24
		155	K J	38	58	57.8	37	0	1	23
		171	K J	22	75	67.5	51	0	0	27
20P	100	207	K J	7	55	62.4	39	0	0	23
		208	K J	7	54	63.1	48	0	0	23
		209	I V	7	52	61.6	52	0	0	24
579T	94	299	K J	1	12	65.1	44	0	0	10
		300	I V	1	19	56.7	46	0	0	10
		301	K J	1	12	60.4	41	0	0	10
129A	94	32	K J	65	21	68.1	51	0	0	13
		36	B M	65	25	64.5	49	0	0	15
		66	K J	18	25	70.1	49	0	0	13
1267A	104	317	I V	1	30	58.0	41	0	0	10
		318	K J	1	30	53.8	46	0	0	10

* In the tables, the letters A, T, or P following culture number designate tooth apex, tonsil and prostate, respectively. Knee joint, intravenous, and bone marrow inoculations are designated K J, I V, and B M, respectively. All rabbits were killed on the day indicated in the column headed "days observed after inoculation" except those marked with an asterisk, these died.

RESULTS

To be reasonably certain that a drop in blood pressure was of significance the extent of fluctuation in the blood pressure in untreated, supposedly normal rabbits was determined. Five hundred and forty-six

determinations of average blood pressure (2,730 separate readings) were made on eighty-two normal rabbits. The mean pressure for the group of eighty-two as determined in the central artery of the ear was 62.5 ± 5.0 mm of mercury. The standard deviation of the pressure was 7.4 mm, and the coefficient of variation was 11.9 per cent. It is of interest that the latter approximates the coefficient of variation of 8.8 to 11.4 per cent found by Alvarez⁵ for human blood pressure. The deviation of individual readings from the mean in no instance exceeded four times the standard deviation, and in only nine instances was it more than three times the standard deviation. Consequently, we

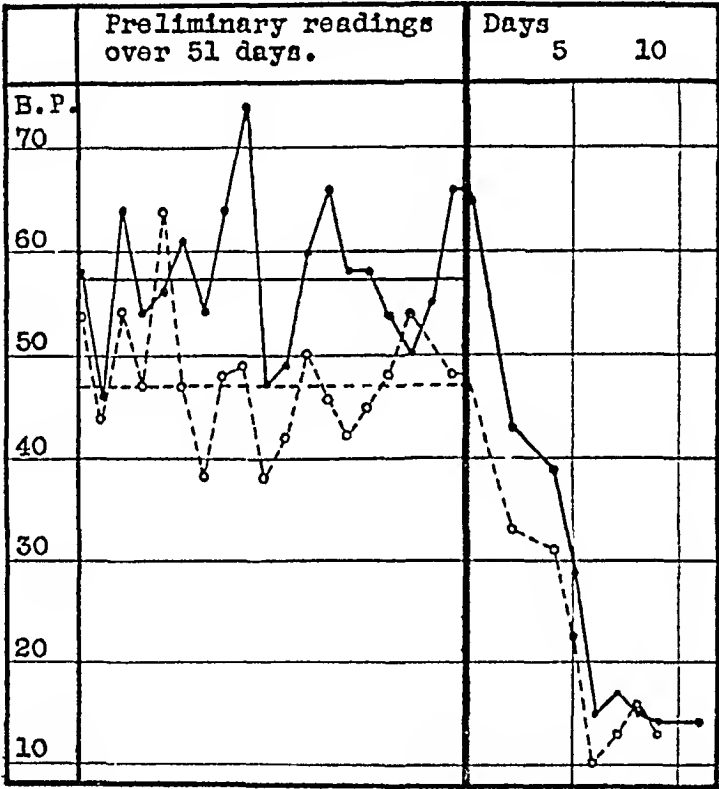


Chart 1—Blood pressure curves of rabbits inoculated with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with low blood pressure. The hollow circle and dash line represent the effect on blood pressure of inoculations into the knee joints of rabbit 34, and the black circle and continuous line represent inoculations into the bone marrow of rabbit 33. The heavy vertical line indicates the time of inoculation.

considered a fall in blood pressure to 32.9 mm (62.5 minus four times the standard deviation 7.4) to be of significance. In the accompanying tables, the number of blood pressure readings falling below 32.9 mm is recorded for each rabbit and the number falling below 40.1 mm is

⁵ Alvarez, Walter C. Blood Pressure in Fifteen Thousand University Freshmen, Arch Int Med 32:17 (July) 1923

also shown. The latter figure represents a fall in blood pressure greater than three times the standard deviation.

Forty-four rabbits were inoculated with sixteen different cultures obtained from persons with a systolic blood pressure under 110 mm. In sixteen of these rabbits (36.8 per cent) the blood pressure subsequently fell to 32.9 mm or less, while in twenty-three (52.2 per cent) it fell to 40.1 mm or less. Of the sixteen cultures used, nine produced a significant drop in blood pressure in one or more rabbits (table 1).

A significant drop in blood pressure was observed in all rabbits inoculated with four cultures, and with the other five cultures a signifi-

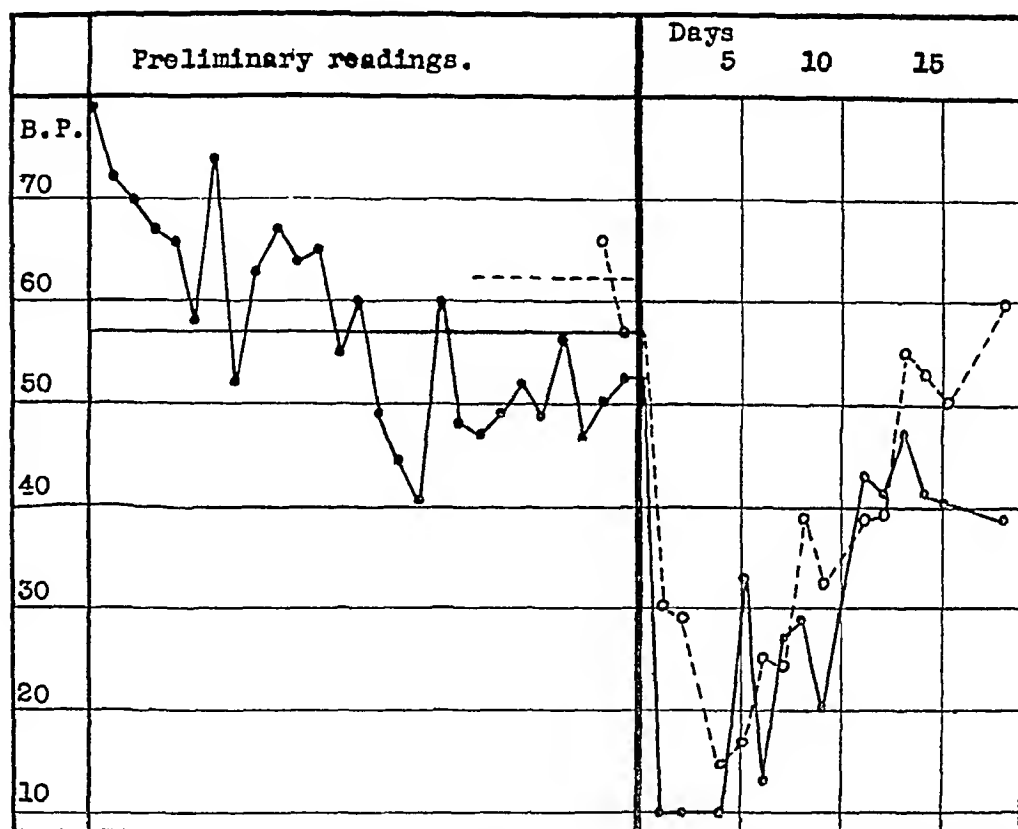


Chart 2—Blood pressure curves of rabbits inoculated intravenously with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with low blood pressure. The hollow curve and dash line represent the reaction in rabbit 54, and the black circle and continuous line, the reaction in rabbit 33. The heavy vertical line represents the time of inoculation.

cant drop was observed in one or more of each group. There was a definite tendency toward uniform results in rabbits inoculated in the same manner with a given culture. Each of two rabbits was inoculated in the knee joints with cultures 1203A, 1070A and 729T, and there was a significant drop in all, while, with one exception, rabbits inoculated intravenously with the same cultures did not show any significant fall in blood pressure. One rabbit each inoculated intravenously with cultures 729A and 246A showed a significant lowering of blood pressure.

TABLE 2—*Results of Inoculation with Bacterial Cultures from Persons with High Blood Pressure*

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 32.9 Mm	Pressure Readings Under 40.1 Mm	Pressure Readings After Inoculation
1203A	226	313	K J	1	36	57.4	25	5	5	12
		314	I V	1	31	60.6	35	0	5	12
		315	I V	1	31	57.0	32	1	5	12
1168T	242	316	K J	1	31	57.4	23	6	7	11
		245	I V	1	31	57.6	17	0	0	9
		246	K J	1	31	61.1	10	0	1	15
1168A	242	247	K J	1	31	56.0	10	0	6	15
		248	I V	1	1*	62.2				6
		249	K J	1	35	59.6	58	0	0	15
		250	K J	1	35	61.2	55	0	0	15

* See footnote table 1

TABLE 3—*Results of Inoculation with Bacterial Cultures from Persons with Normal Blood Pressure*

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 32.9 Mm	Pressure Readings Under 40.1 Mm	Pressure Readings After Inoculation
1214A	130	224	K J	6	19	62.7	49	0	0	14
		225	I V	6	19	63.2	55	0	0	14
		226	K J	6	21	61.0	49	0	0	14
356A	126	271	K J	25	40	51.9	44	0	0	9
		272	K J	25	40	56.5	50	0	0	14
		273	I V	23	40	52.7	15	0	0	14
1274T	98*	206	K J	4	12	59.6	28	0	0	11
		207	K J	4	13	62.7	47	0	0	11
		208	I V	4	13	62.8	47	0	0	11
1952P	124	511	I V		11		69.1	0	0	4
		510	I V		11		62.2	0	0	4
		512	I V		11		57.8	0	0	4
1952T	124	513	I V		12		57.0	0	0	5
		514	I V		4		63.6	0	0	1
		515	I V		14		61.4	0	0	5
93T	124	516	I V		14		65.8	0	0	5
		525	K J	1	2	66.4	68.2	0	0	12
		526	I V	1	15	68.7	61.8	0	0	12
1263T	122	527	K J	1	15	61.8	48.0	0	0	7
		528	I V	1	14	73.8	73.4	0	0	7
		529	K J	1	14	65.7	60.0	0	0	7
1452T	128	530	I V	1	14	67.9	61.4	0	0	7
		531	K J	1	10*	63.5	51.0	0	0	5
		532	I V	1	14	69.0	19.0	0	0	7
29T	126	535	I V	1	14	61.8	51.8	0	0	7
		536	K J	1	15	59.8	59.1	0	0	7
		534	I V	1	15	53.4	54.6	0	0	7
395T	120	533	K J	1	14	66.6	60.6	0	0	7
		537	I V	1	13	61.4	55.2	0	0	6
		538	K J	1	13	63.6	60.2	0	0	6
1319T	118	539	I V	1	13	63.4	59.4	0	0	6
		540	K J	1	13	66.2	58.8	0	0	6

* Boy aged 10

while a change in pressure did not occur in the rabbits inoculated in the knee joints with the same cultures

The blood pressure curves shown in charts 1 and 2 are typical examples of the reaction observed. The results are shown when one rabbit was inoculated in the knee joints and the other in the bone marrow cavity of the tibia (chart 1). Chart 2 shows the pressure when both rabbits were inoculated intravenously. The blood pressure in most rabbits inoculated intravenously fell rapidly and usually reached a low level about the fourth day after inoculation, after which it gradually rose until about the normal level was reached. In rabbits inoculated in the knee joints or in the bone marrow, the fall in pressure occurred more slowly, and the minimum level was not reached before the sixth day, after which the pressure remained low or rose slowly. The behavior of the blood pressure of rabbits 152 and 153, both inoculated in the knee joints with the same culture, was atypical. In neither rabbit was there a significant drop in pressure until the seventeenth day after

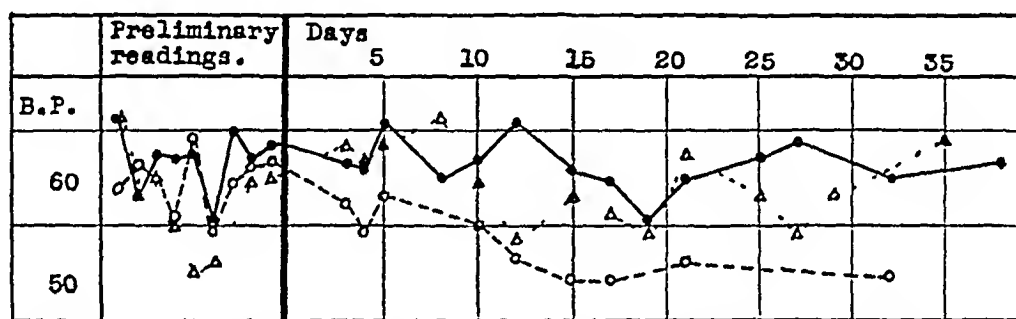


Chart 3—Blood pressure curves of rabbits inoculated with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with normal blood pressure. The black circle and solid line represent the curve of the rabbit inoculated intravenously (R 273), the triangle and dash line represent the blood pressure of rabbit 272, and the hollow circle and dash line, that of rabbit 271, after inoculation into the knee joints. The heavy vertical line indicates the time of inoculation.

inoculation, when it fell from 62 and 63 millimeters to 20 and 32 millimeters, respectively. The pressure remained low in both for about ten days and then rose by roughly half the drop only to fall a few days later to a still lower level, where it remained in both cases until the fifty-eighth day. At this time, a sharp rise in pressure was seen in rabbit 152 followed by another fall and then a rather rapid rise to the normal level, where the blood pressure remained until the rabbit was killed 163 days after the inoculation. On the fifty-eighth day, a slight rise in pressure was also seen in rabbit 153, followed by a fall, then there was another slight rise followed by a fall, which persisted until the animal was killed on the eightieth day after the inoculation. We feel that it is at least plausible to consider that at the periods when the

infecting organisms were active the pressure fell, and as resistance became better and the bacterial activity diminished, the pressure again approached the normal level

Ten rabbits were inoculated with three different cultures obtained from two persons with a systolic blood pressure of over 220 mm. In three of these rabbits (30.0 per cent), there was a significant fall in pressure (table 2)

Thirty-two rabbits were inoculated with thirteen different cultures obtained from twelve persons with normal blood pressures. Significant changes in blood pressure were not noted in any rabbits of this group (table 3). The blood pressure curves of three rabbits inoculated with one of these cultures are shown in chart 3.

COMMENT

We believe that these experiments demonstrate that certain bacterial cultures can produce a marked fall in the blood pressure of rabbits. In the experiments described, if a fall in blood pressure occurred in

TABLE 4—*Summary of Results of Inoculation with Bacterial Cultures*

Blood Pressure of Patients	Cases	Cultures	Cultures Producing Fall in Pressure	Rabbits Inoculated	Rabbits with Pressure Under 20 mm	Rabbits with Pressure Under 40-1 mm
Low	11	16	9	11	16	23
High	2	3	1	10	3	6
Normal	12	13	0	2	0	1

one of a group of animals inoculated with a given culture, a fall was usually observed in all animals inoculated in the same manner. Intravenous inoculations produced a drop in blood pressure which reached a minimum level on about the fourth day, after which, as a rule, the pressure gradually returned to normal. When inoculations were made into knee joints or bone marrow, the fall in blood pressure occurred more slowly, but the pressure remained low for a longer time. It has been our experience that an overwhelming infection is not of itself sufficient to cause a significant fall in blood pressure. We have found the blood pressure of rabbits that had been injected intravenously with enormous doses of streptococci to be between 50 and 60 mm. at a time when they were so near death that they were unable to stand.

It is possible that certain strains of organisms are able to elaborate in vivo a chemical substance responsible for the marked fall in blood pressure which was seen. Koessler, Lewis and Walker⁶ have demonstrated that certain organisms grown in a blood-broth-glycerol-amino-

⁶ Koessler, Karl K., Lewis, Julian H. and Walker, Jennie A. Pharmacodynamic Actions of Bacterial Poison, Arch. Int. Med. 39:188 (Feb.) 1927.

acid medium form substances which cause arterial constriction in vitro and bronchial constriction in the living pithed guinea-pig. They have found that some of these substances behave like histamine and cause constriction of the arteries in vitro and fall in blood pressure in vivo. Further experiments are being carried on in an effort to demonstrate such a substance in cultures the inoculation of which has been followed by a fall in the blood pressure of rabbits.

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THE UTILIZATION OF JERUSALEM ARTICHOKE BY A PATIENT WITH DIABETES

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AND

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The value of Jerusalem artichokes in the dietetic treatment of persons with diabetes mellitus depends on whether the absence of glycosuria is due to actual absorption and utilization of the carbohydrates or to escape from absorption. A patient of one of us has used large quantities of the dried Jerusalem artichoke in his diet for a number of years, and he volunteered to spend his spring academic vacation of 1926 at the New England Deaconess Hospital, subject to a controlled diet and to various physiologic and chemical observations designed to study this question.

The previous literature with respect to the chemistry and metabolic effect of Jerusalem artichokes and inulin has been reviewed in a recent publication by Root and Baker.¹ They gave baked artichokes containing from 31 to 81 Gm of carbohydrate in six cases and determined the respiratory exchange by the gasometer method, finding a rise in respiratory quotients from the first to the sixth hour after ingestion, with an upward tendency with respect to duration. In six diabetic cases, the blood sugar was determined before and after the ingestion of artichokes containing from 37 to 81 Gm of carbohydrate. A slight rise was observed in all cases, with a fall at the end of six hours to values slightly lower than those found before ingestion. These authors drew the conclusion from the respiratory quotients and the blood sugar that the absorption of some reducing sugar due to the taking of artichokes was proved.

OBJECTS AND METHODS OF THE INVESTIGATION

Our object in this investigation was to determine the effects on the course of the respiratory quotient and the gaseous exchange during the day in comparison with the basal metabolism for the day, determined before the first meal, as brought about by the use of a diet in which Jerusalem artichokes furnished the major portion of the carbohydrates. An attempt was also made to determine the amounts of protein, fat and carbohydrate absorbed, as shown by the balance between the intake in the

¹ From the Nutrition Laboratory of the Carnegie Institution of Washington and the New England Deaconess Hospital, service of Dr F P Joslin.

1 Root, H F, and Baker, M L. Inulin and Artichokes in the Treatment of Diabetes, Arch Int Med **36** 126 (July) 1925.

food and the outgo in the feces i.e., the so-called digestion coefficients. Supplementary studies of the blood and urine were also made. From the measurements of the respiratory exchange and the nitrogen in the urine, estimates were made of the amounts of the three foodstuffs catabolized in comparison with the amounts calculated as absorbed from the food ingested. Potato, furnishing an equivalent amount of carbohydrate, was then substituted for the artichokes to see what changes in metabolism would take place, and whether the patient could tolerate the carbohydrate in this form.

The respiratory exchange was determined by the gasometer method a half face mask being used as a breathing appliance and two gasometers connected in such a way that a continuous series of periods of observation could be made. The patient was thoroughly acquainted with the procedure by previous tests. The analyses of air were made by the Haldane portable apparatus and usually by two workers independently, with outdoor air controls, each day before the analyses were begun. Standard methods for the determination of blood sugar, blood carbon dioxide, cholesterol and fatty acids, urinary nitrogen and urinary sugar were used. The food eaten by the patient was duplicated on several days as a composite sample preserved by a substantial addition of xylene, dried and subsequently analyzed. The intention was to obtain a separation of the feces, carmine being used as a marker, but the character and color of the feces were such that the carmine was undetectable, and a separation could not be made. All of the feces voided during the time of the investigation (six days) were collected, preserved with xylene, dried and analyzed. After the samples of foods and feces were partially dried in an oven below 100 C, the remaining moisture was determined by desiccation in a high vacuum at room temperature. The protein was estimated by multiplying the nitrogen by 6.25. A determination of the ether soluble extract was made, and portions of the original dried samples were burned at low red heat in order to estimate the ash. Then the nitrogen-free extract (total carbohydrates) was calculated by adding the protein, moisture, ash and fat and by estimating the balance as total carbohydrates. The reducing sugars and hydrolyzable sugars were extracted and hydrolyzed according to the methods of the Official Agricultural Chemists². The reducing sugars before and after hydrolysis were determined in the extracts by the method of S. R. Benedict³. The heats of combustion of the food composites and the feces were determined with the oxycalorimeter of Benedict and Fox⁴.

2 Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Washington, D. C. 1920, pp. 74 and 95.

3 Benedict, S. R. A Method for the Estimation of Reducing Sugars, *J. Biol. Chem.* **9** 57, 1911.

4 Benedict, F. G., and Fox, E. L. A Method for the Determination of the Energy Value of Foods and Excreta *J. Biol. Chem.* **66** 783, 1925.

REPORT OF CASE

History—The patient, a college professor, developed diabetes at the age of 41 years and 5 months. At the time of the observations here reported, he was 52 years and 8 months old. There was no other case of diabetes in his family. His own past history was unimportant, except for the occurrence of typhoid fever in 1884, 1887 and 1907, and pneumonia. His maximum weight had been 70 Kg in 1888 and in 1915 he weighed 66 Kg. He came under the treatment of Dr. E. P. Joslin on May 5, 1919. His diet and progress since that time are shown in table 1. He was discharged from the hospital in May, 1919, returned on June 19, 1921, and on Sept. 24, 1922, at which time he began taking insulin. He began using Jerusalem artichokes on Sept. 29, 1923. From that time on, he continued to use the artichokes which he learned to dry in order to have a supply all the year. For several months prior to April, 1926, he had been taking the equivalent of nearly a kilogram of fresh artichokes in a dried form per day. He had found by numerous experiments at home that whereas he could take carbohydrate in that form without causing the appearance of sugar in the urine, he could not add carbohydrate in any other form to his regular diet without causing glycosuria.

TABLE 1—*Diet, Body Weight and Condition of Patient no. 1500*

Date	Diet				Body Weight, Kg.	Urinary Sugar	Blood Sugar per Cent	Insulin Units
	Protein Gm.	Fat, Gm.	Carbohydrates Gm.	Calories				
May 1919	60	83	16	1,207	53.5			
June 9, 1919	71	136	50	1,772				
June 19, 1921	64	97	29	1,215		Not sugar free	0.21	
Sept. 24, 1922	52	113	26	1,329	44.5	Sugar free	0.23*	2
Feb. 12, 1924	50	110	63	1,447	55	Sugar free	0.10	21
April 3, 1926	46	63	129	1,267	57.5			26

* Sept. 28, 1922

Diet and Food Intake—The foods eaten daily during the patient's stay of six days in the hospital consisted of the following: from 2 to 4 eggs, 60 Gm. of chicken meat, from 630 to 750 Gm. of 5 per cent vegetables, from 8 to 12 Gm. of butter, 180 Gm. of 20 per cent cream, from 74 to 120 Gm. of washed bran, from 60 to 135 Gm. of mineral oil mayonnaise and 750 Gm. of Irish moss jelly.⁵ On every day but April 7 he used 198 Gm. of dried Jerusalem artichokes, and on April 7 he had 500 Gm. of baked potatoes. The bran was thoroughly washed by the patient to remove starch, made into cakes and dried. The dried artichokes were also prepared by the patient and were brought by him to the hospital. The total hydrolyzable carbohydrates of the dried artichokes was about 50 per cent. A sample of the material sent to us by the patient later gave 2 per cent of reducing sugars and 55 per cent of hydrolyzable sugars, and the heat of combustion was 3.4 calories per gram. The hydrolyzable sugar was alcohol-soluble, apparently present in the form of polymers of levulose and not as inulin.

Food composites were collected on four days, and the amount of protein, carbohydrate and fat (including mineral oil) are shown in table 2, as determined by analysis and calculation. The energy derived from each nutrient is calcu-

5 A subsequent analysis of a composite exclusive of bran, mayonnaise and Irish moss jelly gave protein, 46 Gm., fat, 60 Gm., and carbohydrate, 31 Gm.

lated, and the sum of the calculated calories is compared with the value calculated from the determination by the oxycalorimeter. The computation of the percentages of energy due to each of the three nutrients would result in values too low for protein and carbohydrate and too high for fat, because the total energy is raised by the inclusion of the mineral oil in the composite samples. The presence of mineral oil also complicated the calculation of the energy furnished by fat. The usual value per gram of fat cannot be assigned, as the heat of combustion of mineral oil is higher than fat. There was so much oil in the composite samples that it prevented the drying of the samples, and it was necessary to skim the oil from the surface. Three such samples were obtained, and the heat of combustion was determined by the oxycalorimeter with values of 11.51, 10.64 and 10.35 calories per gram. The average of these three has been used in calculating the energy in the column showing the values for fat. As a check on

TABLE 2—*Weights of Nutrients, and Distribution of Energy in Food Composites and Feces*

Date, 1926	Weights of Nutrients			Division of Carbohydrates			Distribution of Energy			Total Energy Calculated from Sum of Nutrients, Calories	Total Energy Determined by Oxycalorimeter, Calories
	Protein, Gm	Ether Soluble Extract, Gm	Nitrogen Free Extract, Gm	Reducing Sugars,* Gm	Hydrolyzable Sugars,* Gm	Balance, Gm	Protein, Calories	Ether Soluble Extract, Calories	Nitrogen Free Extract, Calories		
Food Composites											
April 3	83	141	285	7	131	147	468	1,525	1,138	3,131	3,199
April 4	75	176	264	43	53	168	422	2,056	1,058	3,536	3,528
April 5	82	130	279	9	113	157	466	1,397	1,117	2,980	3,009
April 7	65	118	259	8†	7†	244	369	1,271	1,037	2,677	2,661
Average per day	76	141	271	17	76	179	431	1,562	1,088	3,081	3,099
Average of 6 days' feces	26	101	66			66	145	1,153	264	1,532	1,621
Average absorption per day	50	40	205	17	76	113	286	409	824	1,519	1,478

* A sample of the dried artichokes gave 2 per cent of reducing sugars and 55 per cent of hydrolyzable sugars. Therefore, 198 Gm of dried artichokes must have supplied nearly all of the sugars.

† Artichokes replaced by potato

the probable accuracy of the calculation of the carbohydrates, the sum of the calories derived from the three nutrients may be compared with that directly determined by the oxycalorimeter. The amounts of carbohydrates in the different days may be taken as probably within 5 per cent of the actual amount present. These carbohydrates include those from bran and the Irish moss as well as those available in the Jerusalem artichokes. The amounts of reducing sugars and total hydrolyzable sugars are also shown in table 2. The total sugars ranged from 93 to 138 Gm, the day on which potatoes were given (April 7) being omitted on this day they were 15 Gm, which is consistent with the difference in composition of Jerusalem artichokes and of potatoes. The carbohydrates, other than sugars, were more than half of the total carbohydrates and on April 7 were 94 per cent of the total carbohydrates. The agreement between the energy calculated from the sum of the values derived from the weights by analysis and that found by the determination by the oxycalorimeter is satisfactory. The greatest difference was on April 3, i. e., 62 per cent and the least on April 4, 0.2 per cent. The average difference was 0.6 per cent.

Composition of Feces and Apparent Absorption of Nutrients—In table 2 is shown also the average daily excretion of unabsorbed nutrients and oil in the feces. As the diet was essentially constant throughout the six days and similar to that the patient usually had, it is felt that there would not be much error in balancing the amount coming from his food previous to the first day with that which is due to the last day's food and which would be voided after he left the hospital. This patient used sufficient bran and mineral oil in his diet to warrant the belief that the passage of unabsorbed material was not unduly delayed. On the contrary, the investigations of Burrows and Farr,⁶ Dutcher, Ely and Honeywell, and Mellanby⁸ and Schlaginweit⁹ indicated an interference with the absorption of fat in the presence of petroleum oil, and this may account for the fact that although 60 Gm of fat was supplied in the diet, only 40 Gm was apparently absorbed. In the calculation of the energy due to fat or oil, the value of 11.47 calories per gram was used, which is the heat of combustion of a mineral oil, because so much of the unabsorbed ether extract must have been due to the mineral oil. The average daily excretion in the feces showed a large amount of ether extract (mineral oil) a smaller amount of carbohydrate and no sugar.

The amounts calculated as absorbed per day give 50 Gm protein, 40 Gm ether extract, and 205 Gm of carbohydrate. Sixty-six per cent of the protein ingested and 76 per cent of the carbohydrates were absorbed, which included all of the sugars and 113 grams of carbohydrates other than sugars. The total energy absorbed was about 1,500 calories. The sugars formed 46 per cent of the total carbohydrates absorbed. If one omits the day on which potato was given, the total sugars ingested were 119 Gm per day and the other carbohydrates were 157 Gm per day. The deduction of unabsorbed carbohydrates gives 119 Gm of sugars and 91 Gm of other carbohydrates absorbed, so that the sugars formed nearly 57 per cent of the retained carbohydrates, which must have come, in the main, from the Jerusalem artichokes. The distribution of energy in the material retained was protein, 19 per cent, fat, 27 per cent, and carbohydrate 54 per cent.

The basal metabolism of an average man of 53 years, 57.5 Kg in weight and 170 cm tall, according to the Harris and Benedict standard, would be 1,350 calories per day. The apparent available energy was 1,500 calories, so that 11 per cent was available for influence of food and activity. A calculation of the energy production is made later in the paper.

Analyses of Blood—The results of determinations of sugar, carbon dioxide content, cholesterol and fatty acids in the blood are shown in table 3. The blood sugar gave normal values on the first day in the hospital but on the next two mornings was slightly higher. On the morning of April 7, it was 0.17 per cent in the postabsorptive condition. On this day the patient was given baked potatoes at his first meal at 9 a. m., and at 12.45 p. m. the blood sugar had risen to 0.24, by 7.15 p. m., it was 0.31 per cent, so that the ingestion of potato, which did not contain any more carbohydrate than he had been having in the form of arti-

6 Burrows, M. T., and Farr, W. K. The Action of Mineral Oil Per Os on the Organism, *Proc Soc Exper Biol & Med* **24** 719 (April) 1927.

7 Dutcher, R. A., Ely, J. O., and Honeywell, H. E. Vitamin Studies. XV. Assimilation of Vitamins A and D in Presence of Mineral Oil, *Proc Soc Exper Biol & Med* **24** 953 (June) 1927.

8 Mellanby, J. Petroleum Emulsion in the Small Intestine, *J Physiol* **64** XXXIII (Dec) 1927.

9 Schlaginweit, E. Untersuchungen über die Darmwirkung des Paraffinum liquidum, *Arch f exper Path u Pharmacol* **124** 59 (July) 1927.

chokes, caused a marked increase in the blood sugar which continued even until the next morning, when it was 0.27 per cent. However, by 2.45 p. m. on April 8, it was back again at the level of the morning of the 7th. The blood carbon dioxide showed little change in the first two days and was not determined again until three days later, when it was lower. Specific changes did not occur in the cholesterol or fatty acids of the blood during the six days.

Urine—The urine was collected at frequent intervals during the six days' stay at the hospital, it was tested for diacetic acid and sugar and the total nitrogen determined. After the patient left the hospital, he collected his urine in twenty-four hour periods and sent specimens on for analysis (table 4). The first four days' urine contained an average of 8.3+ Gm. of nitrogen per day equivalent to 0.15 Gm. per kilogram and no sugar or diacetic acid. The calculated protein catabolized is thus about 52 Gm. per day. On the day of the ingestion of potato, there were two marked changes in the urinary elimination. The potato was eaten at 9 a. m., and the first collection of urine after this was

TABLE 3—*Blood Sugar, Carbon Dioxide Content, Cholesterol and Fatty Acids*

Date, 1926	Time	Sugar, per Cent	Carbon Dioxide, per Cent by Volume	Cholesterol, Mg	Fatty Acids, Mg
April 3	P. A. *	0.08	64	308	495
April 3	12.50 p. m.	0.09	64	332	408
April 4	P. A. *	0.14	64	288	
April 4	9.00 a. m.				308
April 4	9.30 a. m.	0.19	63	280	387
April 4	10.00 a. m.	0.19	61	278	385
April 7	P. A. *				558
April 7	9.40 a. m.	0.17	57	262	
April 7	12.45 p. m.	0.24	58	262	439
April 7	3.15 p. m.	0.28	57	260	466
April 7	7.15 p. m.	0.31		270	
April 8	P. A. *	0.27		308	482
April 8	12.30 p. m.	0.26		262	440
April 8	2.45 p. m.	0.16			
April 9	P. A. *	0.20			

* Postabsorptive, i. e., before breakfast.

at 11.05 a. m., a volume of 93 cc., with 0.3 Gm. of sugar. Collections were again made at 12.39 p. m., 1.29 p. m., 2.47 p. m., 4.22 p. m., 10 p. m., and 7 a. m., on April 8. All of these contained sugar in measurable amounts, the greatest amount occurring in the urine collected at 2.47 p. m., i. e., 2 Gm. The specimens of urine next day showed sugar, including a collection made at 2.48 p. m. After that, sugar was not found on this or succeeding days. After the first meal containing potato, the appearance of sugar in the urine was prompt, and the specimens continued to show the elimination of sugar for more than twenty-four hours afterward. Simultaneous with the elimination of sugar was a striking increase in elimination of nitrogen on April 7 and 8, and 8 and 9. This cannot be explained as the result of increased protein ingestion on April 7 and 8 as the amount was only 65 Gm. as compared with 75 and 83 Gm. on the other days (table 2). It is difficult to explain this increased elimination of nitrogen. These changes in the urine occurred after the ingestion of potato, which contained as nearly as possible the same amount of carbohydrate as was taken on preceding days in the form of artichokes, and the return to a condition of sugar-free urine, and similar elimination of nitrogen accompanied the resumption of artichokes. No other change was made in the treatment. The patient

received the same amount of insulin at the same intervals as on other days. These changes may be mere coincidence, but it hardly seems likely.

Respiratory Exchange—In table 5 is given a summary of the measurements of the respiratory exchange as indicated by the oxygen absorption and the respiratory quotient. The general program of measurements was to have four ten-minute periods in succession in a postabsorptive condition after the patient had ridden from the hospital to the laboratory. He then ate his first meal, which contained practically one third of the day's diet. Measurements were then made on him for six successive periods for the duration of an hour, and then after a half-hour's rest a group of six was made. He then ate his noon meal, and again six periods

TABLE 4—*Statistics of Examinations of Urine*

Date, 1926	Volume, Cc	Diacetic Acid	Nitrogen, Gm	Sugar, Gm
April 3-4	2,160	0	8.1	0
April 4-5	2,680	0	8.3	0
April 5-6	2,270	0	8.0	0
April 6-7	1,700	0	8.9	0
April 7-8	2,427	0	11.8	6.7
April 8-9	2,185	0	10.0	3.5
April 9-10	1,410	0	7.8	0
April 10-11	2,220	0	6.1	0
April 11-12	2,280	0	7.1	0
April 12-13	2,010		5.1	

TABLE 5—*The Pulse Rate, Oxygen Absorption and Respiratory Quotient of a Diabetic Patient During the Day*

Time	April 3			April 5			April 6			April 7			April 8		
	Pulse	Oxygen, Cc	Respiratory Quotient	Pulse	Oxygen, Cc	Respiratory Quotient	Pulse	Oxygen, Cc	Respiratory Quotient	Pulse	Oxygen, Cc	Respiratory Quotient	Pulse	Oxygen, Cc	Respiratory Quotient
Basal 8-9 a m	55	193	0.85	60	196	0.81	66	193	0.87	60	198	0.81	59	190	0.83
10 00-11 00 a m	58	218	0.86	63	224	0.85				67	227	0.88			
11 30-12 30 p m	57	209	0.86	60	220	0.83				65	230	0.88			
1 30-2 45 p m	58	220	0.88	63	209	0.88				64	237	0.90	68	234	0.89
3 00-4 15 p m	56	207	0.91	61	210	0.88				59	225	0.87	64	216	0.88
5 00-5 30 p m													60	216	0.88
6 40-7 30 p m													66	225	0.91
8 00-9 00 p m													59	207	0.90

during the hour were made, followed by a half-hour's rest, and then six more periods were run. This program was carried out on April 3, 5 and 7. On April 6, he felt fatigued, and so measurements were not made other than the four basal periods in the morning. On April 8 the basal periods were made, and the usual morning periods after breakfast were omitted and measurements resumed again after lunch. In addition, between 5 and 5 30 p m, three more periods were made, and after the evening meal ten more periods were carried out in groups of four and six.

Pulse Rate—The basal pulse, with the exception of April 6, was 60 or under. On April 6, it was somewhat higher. After each meal the pulse for the first group was always higher than the basal pulse, falling slightly in the second group in the morning and in one case, April 5, back to the basal pulse. In a similar manner after the afternoon meal, the average pulse was higher than the basal but fell again in the later afternoon group.

Oxygen Absorption The basal oxygen absorption for all five days was within the range of from 190 to 198 cc per minute. After breakfast the oxygen absorption was increased between 7 and 10 per cent and the second group in the morning, with the exception of April 7 dropped but not to the basal figure. The groups in the afternoon gave similar results with the exception of that of April 5 in which the oxygen absorption was lower than those in the morning but not as low as the basal figure. On April 7 the day on which the patient received potato instead of artichokes, the increase in oxygen absorption as well as the pulse rate was more marked than on any other day although in the first group on the afternoon of April 8 the rise in oxygen absorption was nearly as great as on April 7 at the same time. In the three groups of periods on April 8 during the time in which measurements were not made on the other days that is late afternoon and evening the changes were somewhat similar to those produced by the previous meals on the other days.

Respiratory Quotient The basal respiratory quotients were narrow in range and were normal. The first meal on each day produced a slight increase which lasted through both groups of periods in the morning and the second meal caused the respiratory quotient to rise still higher, so that the highest values occurred in the afternoon. The rise of April 7 the day on which the patient

TABLE 6—*Estimation of Heat Production from Respirator, Exchange and Urine*

Date, 1926	Calories Produced				Per Cent Distribution		
	Carbo- hydrate	Fat	Protein	Total	Carbo- hydrate	Fat	Protein
April 3	728	495	223	1,446	50	34	16
April 5	609	520	221	1,350	45	38	16
April 7	733	495	328	1,556	47	31	21
April 8	691	490	275	1,456	47	34	19

received potato was more marked in the morning than on the other days. On April 8 the afternoon periods showed about the same increase and the respiratory quotient was raised to a higher point by the evening meal.

In general then we have a patient who has a normal basal respiratory quotient with an increase in pulse rate, oxygen absorption and respiratory quotient, produced by the ingestion of a mixed meal with a large proportion of carbohydrate about one half of which for four days was in the form of Jerusalem artichokes.

Heat Production—The heat production per day was calculated for the four days on which there were periods of determinations of respiratory exchange other than those of the basal metabolism. To obtain a correct estimate of the metabolism for twenty-four hours when there are only intermittent periods of measurement during the day is always difficult. In this series the basal periods have been used for the time between 10 p. m. and 7 a. m. and the values obtained in the measurements of respiratory exchange during the four days have been apportioned for the rest of the day. To use basal figures for the metabolism during sleep may be questioned, as the metabolism during sleep is undoubtedly depressed. On the other hand it is probably incorrect to assume that the respiratory quotient had dropped to basal at 10 p. m. so that the average respiratory quotient for the day would probably be higher than that which could be derived from the values in table 5. In addition allowance was not made for extra muscular activity although there was some activity other than lying quietly on

the cough in the metabolism experiments. The values for heat production and for energy derived from fat and carbohydrate given in table 6 are therefore minimum values.

For the first two days, the calculated heat productions are almost identical and the last day of the four slightly higher than the first two. On the remaining day, April 7, the heat production was materially higher, and the greatest portion of the increase comes from the protein catabolized. This was the day on which potato was used instead of Jerusalem artichoke. Not only was there a disturbance in the metabolism in that sugar was excreted and protein utilization increased, but the metabolism was raised, and to a slight extent this was carried over to the next day.

The distribution of the energy derived from the three nutrients indicated that about 50 per cent came from carbohydrates, under 35 per cent from fat and from 16 to 21 per cent from protein. There was thus a large proportion from carbohydrate and an adequate proportion from protein. If 10 per cent additional is allowed for extra activity, there would be an increase of about 150 calories a day. If this amount is apportioned to carbohydrate and fat in the ratio of 50:35, there would result an increase of 88 calories in the carbohydrate portion and 62 calories in the fat portion. The percentage due to carbohydrate and fat would be increased, while the percentage due to protein would be decreased. The average energy derived from carbohydrate was 713 calories as a minimum, which would be furnished by 178 Gm. while the addition of 88 calories due to extra activity would increase it 22 Gm., making 200 Gm. as a probable maximum of carbohydrates burned. The food eaten during the period indicated in table 2 contained 271 Gm. on the average, and the amount calculated as absorbed was 205 Gm., so that the diet supplied the patient with an amount of carbohydrate which was about equal to that burned as calculated from the metabolism. It was estimated that about 1,500 calories was furnished by the absorbed food. The minimum energy produced, as calculated in table 6, is under this with the exception of the "potato" day, April 7. If an allowance of 10 per cent is made for extra activity, the energy in the food supplied would be about 100 calories too low.

The main problem in this investigation was whether Jerusalem artichokes supplying a large amount of carbohydrates in the diet of a patient with diabetes were absorbed and utilized in the metabolism. The results indicate that the daily intake of dry nitrogen-free, fat-free substances was 270 Gm., of which 30 Gm. was derived from 5 per cent vegetables and cream. 100 was supplied by artichokes and the remainder consisted of unknown substances from Irish moss and bran, that about 205 Gm. of carbohydrate was absorbed, and that from 175 to 200 Gm. was burned in the body. The results show definitely that Jerusalem artichokes can furnish absorbable carbohydrates which are utilized by a diabetic patient.

SUMMARY

The metabolism of a patient with diabetes mellitus in whose diet Jerusalem artichokes furnished one-half the carbohydrates was studied for six days with reference to the gaseous exchange, absorption of food and composition of blood and urine.

The analyses of composites of the food ingested on four days showed an average intake of 76 Gm. of protein and 271 Gm. of dry nitrogen-free and fat-free substances. On five of the six days, Jerusalem artichokes provided more than 100 Gm. of carbohydrates, supplying about

95 per cent of the hydrolyzable sugar. On one day the artichokes were replaced with baked potatoes containing an equivalent amount of carbohydrates.

The analyses of six days' feces indicated an average daily absorption of protein, 50 Gm., fat, 40 Gm. and carbohydrates, 205 Gm., with a total energy content of about 1,500 calories.

The average basal respiratory quotient was 0.84. The food intake divided into three equal portions during the day produced a rise of the respiratory quotient to 0.91 and a maximum increase in the oxygen consumption of 14 per cent.

Although this patient had been sugar free for some time on a diet in which artichokes furnished the greater portion of the carbohydrates, the substitution of an equivalent amount of carbohydrates in baked potatoes on one day was accompanied by an increased excretion of urinary nitrogen, the prompt appearance of sugar in the urine, a rise in the blood sugar and an increase in the heat production. The resumption of Jerusalem artichokes on the next day was accompanied by a disappearance of urinary sugar, a lowering of blood sugar and a lowering of the metabolism of energy.

A calculation of heat production on four days gave from 1,450 to 1,550 calories per twenty-four hours (minimum, not maximum values), with 50 per cent from carbohydrates, from 32 to 36 per cent from fat, and from 16 to 21 per cent from protein.

The results show that Jerusalem artichokes furnish carbohydrates which can be absorbed and utilized by a patient with diabetes mellitus.

DISEASE OF THE CORONARY ARTERIES

ITS OCCURRENCE WITHOUT GROSS CARDIAC HYPERTROPHY *

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Cardiac hypertrophy is frequently found at autopsy in persons with disease of the coronary arteries. An extracoronary mechanism is nearly always responsible for this hypertrophy. In this report, however, we wish to emphasize that gross cardiac hypertrophy is often absent in disease of the coronary arteries even though other marked pathologic changes of the vessels and heart are present.

The term disease of the coronary vessels as employed here needs clarification. It is, of course, well known that the coronary vessels often appear arteriosclerotic at necropsy. But this condition, in a strict sense, is not a disease, it probably represents a metabolic process assailing many structures, among them blood vessels. The arteriosclerotic alteration of such vessels is, in a certain respect, the testimony and stigma of advancing years. Markedly sclerotic vessels are sometimes seen in comparatively young persons, generally, however, arteriosclerosis occurs in the later decades of life and attacks the arterial tree as a whole or else limits itself to one or more circumscribed arterial circuits, i.e., the cerebral, pulmonary or coronary, and involvement of any of these circulatory systems may persist and may be clinically symptomless.

We are, however, interested in disease of the coronary vessels in the sense that some other factor or process, related to or independent of arteriosclerosis, blocks or narrows the vessels, thus producing pathologic alteration of the muscle of the heart. In many instances, the sclerotic walls of the coronary vessels gradually encroach on the lumen of the vessels, eventually causing obliteration. In other cases a superimposed thrombus occludes a vessel that is already the seat of arteriosclerosis. Here the formation of a thrombus may have resulted from the sclerotic process or may be the product of some independent and unknown phenomenon. In many of these circumstances the muscle of the heart may suffer severely and the damage reveal itself by clinical or graphic manifestations. Such hearts damaged by impaired coronary circulation and altered by attendant injury to the muscle may remain grossly unhyertrophied and even small. This does not call for further comment.

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here, nor do we now raise the question whether disease of the coronary vessels can of itself produce cardiac hypertrophy. Our interest is chiefly in a series of patients on whom observation at autopsy disclosed unmistakable crippling of the coronary vessels by either occlusion or gradual obliteration, associated with much injury to the muscle of the heart, the clinical legends of these patients often indicated interference in the coronary vessels, and at death their hearts were not grossly hypertrophied.

These patients had marked atherosclerosis with slow narrowing or complete occlusion of the vessels. Patients with syphilitic arteritis, productive endarteritis and periarteritis nodosa were excluded. Cases of recent occlusion were not considered. The sclerotic process in all instances involved both the right and the left branches, the left coronary artery was predominantly involved in nine cases, and in four cases the right coronary artery was principally diseased. The effect of the sclerosis varied from marked stenosis and partial occlusion to complete closure. The orifices were greatly narrowed in two cases, and the mouth of the right coronary artery was entirely closed in one case. The gross myocardial changes ranged from small scattered and large confluent areas of fibrosis to various degrees of multiple infarction, two cases showed parietal aneurysms of the ventricular wall.

All these patients had unhypertrophied hearts and thus illustrate the contention that *indisputable and advanced coronary disease need not lead to gross cardiac hypertrophy*.

This is not a new view, but we feel that it deserves emphasis. However, the literature, in general, does not contain many definite references on this subject. As far back as 1882, Huber¹ stated that hypertrophy of the left ventricle "bears no relation to myocardial and coronary disease." In more recent years, occasionally one comes on a reference to a small unhypertrophied heart found at autopsy in the presence of coronary thrombosis or closure by an obliterating process. Thus, Faulkner, Marble and White² observed the heart unhypertrophied in three out of a total of thirty cases in which there was complete or practically complete occlusion. Herrick³ published three reports of necropsy in patients with coronary thrombosis, in two of whom the hearts were normal in size. Acker⁴ described a single similar case. Hamman⁵

1 Huber, K. Ueber den Einfluss der Kranzarterienerkrankungen auf das Herz und die chronische myocarditis, Virchows Arch f path Anat **89** 236, 1882.

2 Faulkner, J. M., Marble, H. C., and White, P. D. Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, J A M A **83** 2080 (Dec 27) 1924.

3 Herrick, J. B. Thrombosis of the Coronary Arteries J A M A **72** 387 (Feb 8) 1919.

4 Acker, R. B. Delayed Death in Coronary Thrombosis J A M A **73** 1692 (Nov 29) 1919.

5 Hamman. Symptoms of Coronary Occlusion, Bull Johns Hopkins Hosp **38** 273, 1926.

*Observations in Nineteen Cases of Advanced Disease of the Coronary Arteries
with Coexisting Marked Myocardial Changes (in Seventeen Cases) but
Without Gross Hypertrophy of the Heart*

Age, Year	Sex	Weight of Heart, Gm	Coronary Vessels	Myocardium
43	M	200	Orifices narrowed by intimal thickening and arteries on section show numerous scattered areas of calcification with partial stenosis of lumen	Not described
47	M	270	Descending branch of left coronary vessel shows extensive changes in its wall intima is ulcerated small adherent mural thrombi	Gravish fibrous scars with scattered streaking in the muscle
58	M	200	Tortuous with scattered calcified plaques and in some places stenosis	Decidedly browner than average
58	F	320	Marked atheromatous involvement with slight stenosis, right orifice greatly narrowed, entire vessel small	Marked fibrosis left ventricle, near apex, area 2 cm in diameter in which muscle is replaced by fibrous tissue
61	M	300	Marked diffuse thickening, scattered atherosclerotic plaques in intima with marked stenosis of lumen in places	Fibers coarser than average
61	M	400	Mouth of right coronary vessel completely obstructed, left coronary vessel completely obstructed by calcified atherosclerotic process	Wall of left interventricular septum soft and possibly infarcted and necrotic
65	M	340	In numerous areas arteries pipestem in character with considerable stenosis of lumen in portions	In left myocardium large firm pearly gray area replacing muscle
65	M	300	Pipestem with considerable stenosis in places	Architecture of left myocardium coarse
65	M	200	Anterior descending branch of left coronary vessel completely occluded by small atherosclerotic plaques	Old infarct of left ventricle apex
66	F	220	Lumen of right coronary vessel completely obliterated by soft atheroma	Extensive fibrous streaking several small foci of necrosis near apex
66	M	260	Markedly sclerotic with narrowed lumens	Slight fibrosis about the small vessels
67	F	200	Marked arteriosclerotic involvement and almost complete occlusion of small branch of right coronary vessel	In anterior half of apical region of left ventricle large healed infarct
67	M	340	Marked narrowing by arteriosclerotic plaques with complete occlusion in one area	Moderate dilatation of left ventricle due to marked thinning out of wall in posterior part beginning at interventricular septum and involving half of circumference of left ventricle
68	M	280	Marked atherosclerotic plaques in both vessels, lumen of branch to left ventricle practically obliterated at one point by extensive calcified plaque	Musculature pale reddish brown a few gray translucent flecks replacing muscle cells
70	F	270	Lumen of left coronary vessel considerably stenosed in places	Slight fibrosis of left myocardium
75	F	300	Moderate atheromatosis with thickening circumflex branch to left border of heart shows marked calcification with practically complete occlusion	Pale, brown slight fibrous streaking about small vessels
75	F	350	Marked atherosclerotic involvement with stenosis	Fine linear fibrous streaking
91	F	280	Pipestem with marked stenosis of lumen	Fibers coarse
96	F	300	Marked atherosclerotic thickening with partial occlusion	Not described

stated that the area of cardiac dulness need not be enlarged in persons with coronary occlusion. Nathanson⁶ reviewed 113 cases of severe coronary disease with marked narrowing and partial obliteration of one or more large arteries with well defined changes in the heart muscle, and in forty-five cases the heart was not enlarged, weighing 400 Gm or less. In a paper published this year on cardiac infarction and coronary thrombosis, Parkinson and Bedford⁷ made the casual statement that "cardiac enlargement is not a feature," though they were of the opinion that coronary disease alone can cause some degree of hypertrophy. Experimentally, Hamburger, Priest and Bettmann⁸ did not observe hypertrophy of the heart six months after the artificial introduction of lycopodium spores into the coronary vessels.

It would lead us too far afield to speculate on the causes for this absence of hypertrophy. We wish to indicate, however, that the occurrence of hypertrophy may bear some relation to the ability of the heart to develop an adequate collateral circulation. This ability is variable, as has been demonstrated by anatomic studies. Thus, Gross⁹ found that the heart is abundantly provided with capillary and precapillary anastomoses which are normally not in use and that these are inadequate for emergencies but may become adequate when the coronary obstruction is gradual. More recently Kugel¹⁰ demonstrated a constant interauricular coronary vessel that is possibly capable of enlarging and carrying on the circulatory needs when any of the major branches suffer. Furthermore Oberhelman and LeCount¹¹ noted that in hearts with extensive myocardial changes and with incomplete or total occlusion of one or more coronary arteries, abundant collateral circulation was present. The more gradual the occlusion, the more marked was the compensatory anastomoses that developed. Benson and Hunter¹² directed attention to the frequent occurrence of supernumerary coronary orifices in persons with coronary arterial disease, such supernumerary openings conceivably functioning as sources for collateral circulation.

6 Nathanson, M. H. Diseases of the Coronary Arteries, *Am J M Sc* **170** 240, 1925

7 Parkinson, John, and Bedford, D. Evan. Cardiac Infarction and Coronary Thrombosis, *Lancet* **1** 5, 1928

8 Hamburger, Walter W., Priest, Walter, S. and Bettmann, Ralph B. Experimental Coronary Embolism. *Am J M Sc* **170** 168, 1926

9 Gross, L. The Blood Supply to the Heart in Its Anatomic and Clinical Aspects, New York, Paul B. Hoeber, 1921

10 Kugel, M. A. An Important Anastomotic Blood Vessel in the Auricle of the Human Heart, *Proc Path Soc.*, Nov 10, 1927

11 Oberhelman, H. A., and LeCount, E. R. Variations in Anastomosis of Coronary Arteries and Their Consequences, *J A M A* **82** 1321 (April 26) 1924

12 Benson, R. L., and Hunter, W. C. The Pathology of Coronary Arterial Disease, *Northwest Med* **24** 606 (Dec.) 1925

Accordingly, the capacity of a heart to produce and develop collateral circulation in the face of gradual interference with coronary flow may possibly depend on the anatomic arrangement of the coronary vessels—in other words, on a congenital endowment of pattern and of potential development for coronary anastomoses. When adequate collateral circulation is established, one would not expect cardiac hypertrophy as a consequence to disease of the coronary arteries. When seemingly unexplained hypertrophy accompanies disease of the coronary arteries, one would search for an insufficient, undeveloped collateral coronary circulation.

CONCLUSIONS

1 In cases of marked disease of the coronary vessels, together with a diseased heart on gross examination, the heart was found to be unhypertrophied and even small as revealed at autopsy in the nineteen cases we have tabulated.

2 We had two patients with disease of the coronary arteries in whom clinical manifestations and roentgen-ray evidence pointed to cardiac enlargement. These hearts were dilated, they should not mistakenly be considered hypertrophied.

3 It may be that in the patients with disease of the coronary arteries in whom the heart remained small, the organ failed to hypertrophy because it possessed a potential mechanism ready to function through adequate collateral channels whenever the coronary circulation was gradually blocked or impeded.

ALKALOSIS IN PATIENTS WITH PEPIC ULCER *

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Although toxic symptoms in certain patients being treated for peptic ulcer were observed by Sippy and his co-workers and some study of the blood chemistry had been carried out in a considerable number of these patients, the results were apparently not considered of sufficient importance to warrant their publication. The first observations concerning the intoxication produced by the administration of large amounts of alkali in the Sippy treatment to be recorded in detail were those of Hardt and Rivers¹ in 1923. They pointed out that "patients with duodenal ulcer treated by the Sippy method may develop definite symptoms of toxemia associated with renal changes, increased blood urica, and normal or increased carbon dioxide combining power of the plasma", they asserted also that "patients with duodenal ulcer and renal complications are more inclined to develop these toxic manifestations and to a much greater degree". Shortly after the report of Hardt and Rivers, another paper appeared from the Mayo Clinic by Brown, Eustermann, Hartman and Rowntree,² in which the authors carefully discussed the toxemia occurring in pyloric and in duodenal obstruction. A detailed study of eleven cases was presented in which, as the result of organic obstruction or of anatomic or physiologic stasis in the duodenum, duodenal toxemia developed. They stated "Duodenal toxemia is characterized by a clinical syndrome, by urinary changes, by pathognomonic changes in the chemistry of the blood by decreased renal function, and in case of death by pathologic changes in the kidney". The increased carbon dioxide combining power of the plasma with low plasma chloride was regarded as indicating the existence of this

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1 Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following the Treatment of Peptic Ulcer, *Arch. Int. Med.* **31** 171 (Feb.) 1923.

2 Brown, G. E., Eustermann, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tectany, *Arch. Int. Med.* **32** 425 (Sept.) 1923.

toxemia, and when this was associated with evidence of renal insufficiency, increased blood urea, etc., the diagnosis was considered definite. These authors regarded the degree of chemical disturbance as reflected evidence of the extent of the damage.

When one compares the symptomatology of duodenal toxemia resulting from obstruction with the toxemia encountered in the alkali treatment of persons with peptic ulcer, one is struck by their similarity and is inclined to wonder if possibly the alkalosis is not quite as important an etiologic factor in the toxemia of duodenal obstruction as the supposed specific toxin absorbed from the gastro-intestinal tract.

Previous to the publication of Hardt and Rivers' ¹ paper, toxic manifestations following the administration of sodium bicarbonate had been reported by several investigators, notably Howland and Marriott, Harrop ⁴ and Grant ⁵. One of Grant's patients was undergoing Sippy treatment for peptic ulcer. This patient developed symptoms of alkalosis and tetany and had a carbon dioxide combining power of 91 per cent by volume.

Shortly after the publication of the paper by Hardt and Rivers papers appeared by Kantor ⁶ and by Shattuck, Rohdenburg and Booher ⁷ in which an effort was made to neutralize the hydrochloric acid by other antacids than sodium bicarbonate. Following the suggestion of Greenwald, ⁸ tertiary phosphates of magnesium and calcium were employed. Symptoms of alkalosis were not observed, although these gastric antacids were shown to act efficiently in neutralizing the hydrochloric acid. In the six cases carefully studied by Shattuck, Rohdenburg and Booher the p_{H} and carbon dioxide remained essentially normal. Two patients with peptic ulcer who developed typical symptoms of alkalosis under Sippy management are described by Shattuck.

It is of interest that several years earlier a considerable number of estimations of carbon dioxide were made by one of us (M) on patients of Dr. Shattuck under Sippy management. At that time we did not encounter a single patient in whom the carbon dioxide was

3 Howland, John, and Marriott, W. M. Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, *Quart J Med* **11** 289 (July) 1918.

4 Harrop, G. A. The Production of Tetany by the Intravenous Infusion of Sodium Bicarbonate, *Bull Johns Hopkins Hosp* **30** 62 (March) 1919.

5 Grant, S. B. Tetany. A Report of Cases with Acid-Base Disturbance, *Arch Int Med* **30** 355 (Sept) 1922.

6 Kantor, J. L. Antacid Gastric Therapy with Special Reference to the Use of Neutral Antacids, *J A M A* **81** 816 (Sept 8) 1923.

7 Shattuck, H. F., Rohdenburg, E. L., and Booher, L. E. Antacids in the Medical Management of Peptic Ulcer, *J A M A* **82** 200 (Jan 19) 1924.

8 Greenwald, I. Gastric Antacids which Cannot Act as Systemic Alkalis, *Proc Soc Exper Biol & Med* **20** 436 (May) 1923.

notably high, possibly for the reason that all bloods were taken in the morning (table 3), although this was the particular object of those determinations. We were then aware that many persons with ulcer showed evidence of impaired renal function⁹

The earlier reports on alkalosis did not include the estimation of the blood p_H , although the carbon dioxide combining power was found high when estimated. Binger, Hastings and Neil¹⁰ were apparently the first to determine the blood p_H in a case of alkalosis due to the administration of sodium bicarbonate. They found a p_H of 7.55, thus proving the presence of an uncompensated alkalosis. A year later Kast, Myers and Schmitz¹¹ reported observations on twenty patients with alkalosis, in ten of whom the alkalosis was due to the administration of sodium bicarbonate. Determinations of the blood p_H were made in all cases, the highest figure being 7.6. Four of the patients had peptic ulcers and were undergoing Sippy treatment.

Ellis¹² presented a discussion of four cases of alkalemia, two being due to overdosing with sodium bicarbonate. He stated

The symptoms of poisoning with sodium bicarbonate as given by Hardt and Rivers are in agreement with those noted in these cases. The patients are unduly introspective and nervous. They are irritable and complain of trifles. There is headache, nausea and vomiting, dizziness, vertigo and lightheadedness. They complain of aching pains in the muscles and joints. There is weakness followed by absolute prostration. They become apathetic, drowsy and are aroused with difficulty, and finally tetany and convulsions supervene.

McVicar,¹³ following the work of Brown, Eustermann, Hartman and Rowntree at the Mayo Clinic, reported a study of thirty cases of obstruction in the upper gastro-intestinal tract, and emphasized the value of a characteristic blood chemistry, namely, the rise in the blood urea and carbon dioxide and the fall in the plasma chloride, in the diagnosis, prognosis and treatment. He pointed out that tetany may be anticipated when the carbon dioxide combining power of the plasma is found to be above 100 per cent by volume.

9 Myers, V. C. Chemical Changes in the Blood in Disease. I. Nonprotein and Urea Nitrogen, *J. Lab. & Clin. Med.* **5**:420 (April) 1920.

10 Binger, C. A. L., Hastings, A. B., and Neil, J. M. Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, *Arch. Int. Med.* **32**:145 (Jan.) 1923.

11 Kast, L., Myers, V. C., and Schmitz, H. W. Clinical Conditions of Alkalosis, *J. A. M. A.* **82**:1858 (June 7) 1924.

12 Ellis, A. W. M. Disturbance of the Acid-Base Equilibrium of the Blood to the Alkaline Side. Alkalemia, *Quart. J. Med.* **17**:405 (July) 1924.

13 McVicar, C. S. A Discussion of the Clinical and Laboratory Findings in Certain Cases of Obstruction in the Upper Gastro-Intestinal Tract. The Role of Blood Chemistry in Diagnosis, Prognosis and Treatment of this Condition, *Am. J. M. Sc.* **169**:224, 1925.

Extraordinary "nervous and mental symptoms due to alkalemia and renal insufficiency, following obstruction in the region of the pylorus and the alkaline treatment of duodenal ulcer" have been reported by Houghton and Venables¹⁴ Uremic symptoms with epileptiform convulsions in pyloric obstruction in patients in whom alkalis were not used were attributed by Houghton to loss of hydrochloric acid in the vomitus and a toxic degenerative nephritis with retention of nitrogen These authors apparently emphasized the nitrogen retention in the blood rather than the alkalemia Their laboratory data include only figures for the blood urea which was elevated in all cases The toxic nephritis has been attributed by various authors to a specific toxin entering the circulation from the wall of the obstructed duodenum The increase in the urea and nonprotein nitrogen in the blood, however, has been observed in patients both with and without any obstruction in whom marked alkalosis was present There was obstruction in only one of the seven cases reported by Venables It seems likely that at least a part of the increase in the nonprotein nitrogen is due to a systemic change with excessive protein destruction rather than the result of renal retention, though in the most severe forms of alkalosis a well defined nephritis occurs as a part of the intoxication

Last year Jordan¹⁵ reported observations on the carbon dioxide chloride and calcium content of the blood of forty-one patients with peptic ulcer under Sippy treatment She concluded

It is suggested by the estimations made that the acid-base equilibrium is at first somewhat disturbed by the influx of alkalis, but, within a few days, levels of chloride and carbon dioxide content which approach normal are reached, and in the large majority of cases there is no chemical or clinical disturbance due to alkalosis In the small percentage of cases that show clinical signs of alkalemia the carbon dioxide content shows a marked rise, the calcium content tends to rise, and the plasma chloride to diminish The level of carbon dioxide content at which symptoms appeared in these cases is 70 per cent by volume

Koehler¹⁶ recently reported some interesting observations on four patients with lead poisoning who were alkalinized for a considerable

14 Hurst, A F Houghton, L W, Venables, J F, and Lloyd, N L Nervous Symptoms Due to Alkalaemia and Renal Insufficiency Following Obstruction in the Region of the Pylorus and the Alkaline Treatment of Duodenal Ulcer Introduction (Lloyd) A Three Cases of Toxaemia Following Obstruction Near the Pylorus (Houghton) B Seven Cases of Alkalosis Following Alkaline Treatment of Duodenal Ulcer (Venables) C Two Cases of Pyloric Obstruction with Alkalemia and Renal Insufficiency but No Nervous Symptoms (Lloyd), *Guy's Hosp Rep* **75** 147, 149, 152, 157 (April) 1925

15 Jordan, S M Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, *J A M A* **87** 1905 (Dec 4) 1926

16 Koehler, A E The Effect of Acid and Base Ingestion upon the Acid-Base Balance, *J Biol Chem* **72** 99 (March) 1927

period Forty grams of sodium bicarbonate or an equivalent amount of sodium citrate were used daily With this therapy, a blood p_H of 7.50 to 7.55 could be maintained for several weeks The accompanying carbon dioxide content varied between 65 and 70 per cent by volume The amount of sodium bicarbonate used in the routine Sippy treatment, that is, in the average case, is a little less than that used by Koehler in the treatment of persons with lead poisoning but the total amount of alkali used in the treatment of persons with ulcer is at least from 10 to 20 per cent greater That the symptoms of acidosis and alkalosis may be similar was pointed out by Myers and Booher,¹⁷ and Koehler¹⁸ strongly emphasized this point He stated "In our study practically every symptom elicited during acidosis was noted during alkalosis, namely, loss of appetite, lassitude, listlessness, headache, nausea and drowsiness"

PRESENT STUDY

This study was primarily undertaken to determine the effect on the blood chemistry produced by the alkalis administered in the treatment of persons with peptic ulcer Other incidental problems came up in the course of the study We were interested in finding out how frequently the clinical symptoms of alkalosis accompanied definite changes in the acid-base equilibrium We also made some study of the effect of the various alkalis used in the routine treatment, the effect of vomiting and aspiration of large quantities of gastric juice and the shift of the acid-base balance after relief of pyloric obstruction by gastro-enterostomy Consideration was also given to the blood chemistry in conditions other than ulcer of the stomach and duodenum In spite of the fact that there are only a few of these cases, they are of interest in this connection because of one or more symptoms in common with certain forms of peptic ulcer Some of these results are included at the end of the general table (table 1)

The patients used for this study were chiefly persons from the medical wards who were receiving treatment for peptic ulcer In general, when surgical treatment offered more than medical treatment, operations have been advised or urged Obstruction at the pylorus has been an indication for surgical treatment as a rule, but when operation was refused these patients with obstruction were necessarily treated medically and some of them, especially when they suffered from pain, received alkalis In our treatment of patients with peptic ulcer we have attempted to individualize as much as possible¹⁸

17 Myers, V. C., and Booher, L. E. Some Variations in the Acid-Base Balance of the Blood in Disease, *J. Biol. Chem.* **59**: 699 (April) 1924

18 Gatewood, W. E. Cooperation in the Management of Peptic Ulcer, *J. Iowa State M. Soc.* **16**: 23 (May) 1926

TABLE 1—Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Receiving Alkalis, Including Observations on Several Miscellaneous Conditions

Case	Age	Sex	Date, 1926-1927	Electro- metric pH	Carbon Dioxide Con- tent, Cc	Plasma Chlorine as Sodium Chloride, Mg	Serum Sodium, Mg	Hemo- globin, Gm	Non protein Nitro- gen, Mg	Ure- a Nitro- gen, Mg	Diagnosis, Comment
1 G L	53	M	Jan 5, a.m. Jan 24, 1 m Feb 23, p.m.	7.6+* 7.37 7.43*	120.0 71.1 57.0	550		11.7		22.8	Duodenal ulcer with obstruction No alkalis marked symptoms of alkalosis, gastro-enterostomy, Jan 12, 1927, markedly improved before operation by intravenous injection of 10 per cent dextrose in isotonic salt solution
2 C D	66	M	Nov 1, 1 m Nov 8, a.m. Nov 13, 1 m	7.18 7.37 7.58	77.8 78.7 75.8	680 572 594		10.9 9.7 6.1		18.1 18.2 19.1	Duodenal ulcer Mild symptoms after routine alkalis for eight days
3 R P	31	M	Dec 10, a.m. Dec 12, a.m. Dec 13, a.m. Feb 11, p.m. Feb 12, a.m. Feb 12, p.m. Feb 21, p.m. Feb 23, a.m. Mar 18, p.m. Mar 19, 1 m	7.38 7.48* 7.54 7.76* 7.71 7.71* 7.71* 7.70* 7.70* 7.39*	68.8 81.5 74.4 71.9 59.4 55.0 76.0 33.2	575 475 574 563 591 540 549	323 359 326 332 326	17.1 14.5 16.1 13.8	40.8 11.2 25.0	13.9	Duodenal ulcer December 10, before alkalis December 13, after routine alkalis for three days, nervousness, headache, muscle twitching, vomiting February 11, on routine alkalis, marked symptoms February 23, on eukened magnesia and calcium carbonate, no symptoms
4 D B	48	F	Feb 18, a.m. Feb 23, p.m. Feb 26, a.m. Mar 2, a.m. Mar 22, p.m. April 22, p.m. April 23, a.m.	7.10 7.51* 7.53 7.41 7.37 7.52* 7.49*	69.4 71.0 71.0 55.1 59.8 68.3 63.6	549 549 544 570 540 576	354 361 312	9.6 14.1	35.3 30.8 36.4		Duodenal ulcer with slight obstruction February 18, before alkalis February 25 after routine alkalis for one week, marked symptoms March 2, after eukened magnesia and calcium carbonate only, no symptoms
5 C D	43	M	Nov 19, a.m. Nov 26, a.m. Dec 7, a.m.	7.12 7.44 7.11	76.8 77.9 71.1	519 590 575	322	15.2 12.9		21.2	Duodenal ulcer with slight obstruction On November 19, marked symptoms before alkalis November 26 no symptoms after routine alkalis for eleven days
6 C S	30	M	Nov 16, a.m. Nov 18, a.m. Nov 30, a.m. Nov 30, p.m. Dec 31, a.m.	7.13 7.39 7.52 7.49 7.29*	69.2 60.7 73.0 72.1 58.9	575 594 588 600	361	12.1		22.9	Duodenal ulcer with obstruction November 16, before alkalis, no symptoms November 30 after eukened magnesia and sodium carbonate only for four days, no symptoms, gastro-enterostomy, December 11
7 W W	67	M	Nov 25, a.m. Nov 30, a.m. Nov 30, p.m. Dec 31, a.m. Feb 5, a.m.	7.41 7.50 7.52 7.45* 7.41*	63.1 68.3 77.7 57.9 51.1	613 550 512 538	310 250 303 308	9.5 9.0 10.5	38.2 33.0 1.8 8.7 27.9		Gastric ulcer with slight obstruction November 25, no symptoms before alkalis November 30, marked symptoms after five days of alkalis resection and gastro-enterostomy, December 7, entero-enterostomy January 7

8	F	H	27	M	Jan 25, a m April 21, p m April 22, a m	7:56 7:52* 7:16*	67.3 69.2 61.7	577 613	324	117	39.3		Diodenal ulcer alkalosis	Routine alkalis begun January 21, no symptoms of
9	A	C	75	M	Nov 10, a m Nov 15, a m Nov 22, a m Dec 6, a m June 7	7:10 7:17 7:51 7:30 7:18*	18.5 57.0 60.7 18.5 59.8	600 590 597	308	107	32.3	10.9	Pyloric ulcer with marked obstruction enriched magnesium and calcium carbonate, moderate symptoms, November 22	November 15, after five days
10	D	H	70	M	Nov 22, a m Nov 30, p m	7:51	72.1 65.5	550 559	300	7.3		22.5	Gastric ulcer, marked obstruction moderate symptoms of alkalosis, died, Dec 2, 1927	Marked vomiting, no alkalis
11	A	N	42	M	Mar 25, a m April 1, p m April 2, a m	7:15* {7:51* {7:13*	57.9 64.5 61.7	550 600	323	112	32.1		Gastric ulcer	Routine alkalis, March 25, 1927, no symptoms
12	L	O	34	F	Nov 10, a m Nov 23, a m Dec 1, a m Dec 16, a m	7:19 7:13 7:51*	76.0 61.5 68.3 66.1	575 600 189	397	13.3 12.4	35.9 31.4		Duodenal obstruction, very marked obstruction from November 9 to 21, then stopped, moderate vomiting, mild symptoms of alkalosis	Routine alkalis
13	O	I	34	M	Mar 8, a m Mar 8, p m	7:15* 7:51*	68.3 71.0	550	306	13.8	37.5		Duodenal ulcer	March 8, after routine alkalis for eight days, no symptoms
14	R	P	20	M	Jan 28, a m Feb 17, a m Mar 12, a m Mar 12, p m Mar 25, p m Mar 26, a m May 1	7:44 7:36 7:42* 7:13* 7:50* {7:38* 7:16*	74.0 62.6 61.7 58.9 69.0 68.0 59.8	563 588	343 317	14.1 13.8 14.6	30.6 33.0 31.9		Duodenal ulcer January 28, after six weeks of routine alkalis, routine alkalis continued throughout entire period, no symptoms	
15	I	I	30	M	Dec 2, a m Dec 31, a m	7:49 7:33*	71.9 64.5	550 525	322 283	15.2	33.5 28.0	15.5	Duodenal and gastric ulcer December 8, no symptoms of alkalosis, resection and entero- anastomosis, Dec 10, 1926	Routine alkalis from November 30 to
16	C	R	55	M	Jan 31, a m Feb 5, a m Feb 11, a m Feb 11, p m	7:42 7:17 7:14* 7:19	57.0 65.5 65.5 73.0	600 588 600 550	306 302 323 350	10.9 11.4 10.6 10.1	30.9 35.3		Duodenal ulcer of alkalosis	Routine alkalis from February 1 to 5 no symptoms
17	G	S	54	M	Feb 18, a m Mar 2, p m Mar 3, a m Mar 11, a m Mar 11, p m	7:38 {7:39 {7:30* 7:36 {7:19	58.9 63.5 59.8 65.5 71.9	588 611 631 593 562	337 306 313 334 325	12.3 12.8 13.1	35.7 36.3 32.1		Duodenal ulcer, slight obstruction (15 Gm) and calcium carbonate, 160 grains (10 Gm) from Feb- ruary 2 to March 4, enriched magnesium 70 grains calcium carbo- nate, 80 grains (5.2 Gm) and sodium bicarbonate, 310 grains (20 Gm), no symptoms of alkalosis, Mosenthal test negative	
18	I	II	41	M	Mar 29, 1 m Mar 29, p m Mar 31, a m April 22, p m	7:37* 7:19* 7:19* 7:34*	59.8 69.2 68.3 72.1	580 575	360	13.8 13.5	42.5 38.7		Duodenal ulcer	Routine alkalis from March 21 to discharge, no symptoms

* Determination made colorimetrically

TABLE 1—Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Recovering Alkalosis, Including Observations on Several Miscellaneous Conditions—Continued

Case	Age	Sex	Date, 1926-1927	Licetrometric pH	Carbon Dioxide Content, Cc	Plasma Chlorine as Sodium Chloride, Mgr	Serum Sodium, Mgr	Hemoglobin, Gm	Non-protein Nitrogen, Mgr	Urea Nitrogen, Mgr	Diagnosis, Comment
19 C P	35	M	Dec 13, a m Dec 31, a m	7.18 7.39	75.8 71.1						Routine alkalis from December 3 to December 21, then none, no symptoms of alkalosis
20 J J	27	M	April 11, p m April 12, a m	7.18* 7.10*	84.5 72.1	781		15.0	41.9		After routine alkalis for eight days, no symptoms
21 O P	34	F	May 12, 1925 May 20, 1925 June 12, 1925 June 29, 1925 June 26, 1925	7.11* 7.18* 7.23* 7.29* 7.15*	91.0 91.0 86.0 79.0 82.0	556 610		9.2 7.1 7.5 7.6 11.0	21.0 29.0 48.0 10.2 28.7	11.1 29.0 29.1 27.1	Duodenal ulcer, very marked obstruction. No alkalis except from May 8 to May 10, calcined magnesias, 75 grains, and calcium carbonate, 170 grains, moderate symptoms of alkalosis from May 10 to May 20, gastroenterostomy May 22, all urine examinations negative
22 L H	33	M	Feb 8, a m Feb 17, p m Feb 18, 1 m Feb 21, p m Feb 22, a m	7.13 7.11 7.13 7.16* 7.39*	63.5 65.5 65.5 77.7 65.5	613 557 562	322 332 338				Duodenal ulcer. February 10 to February 17, on calcined magnesias, 70 grains, and calcium carbonate, 120 grains, February 18 to February 21, calcined magnesias, 30 grains, calcium carbonate, 60 grains, and sodium bicarbonate, 250 grains, no symptoms to February 18, severe headache, February 18 to February 21
23 C L	52	M	Nov 21, a m Dec 13, 1 m	7.15 7.16	67.3 68.3	606 600	314 329	13.9 15.2	46.4 32.2	10.8	Routine alkalis from November 23 to December 17, no symptoms
24 J L	46	M	Dec 13, a m Dec 20, p m	7.10 7.16	56.0 71.9	587 575	315 340	1.1 13.2	38.7 15.1	16.2	Duodenal ulcer, marked obstruction. Routine alkalis from December 11 to December 20, no symptoms
25 L R	27	M	Dec 7, a m	7.16	72.1	500	328	1.3	35.1		Duodenal ulcer. After five weeks of routine alkalis, no symptoms
26 M K	26	M	Nov 27, a m	7.16	61.7	590	311	14.1	41.7		Duodenal ulcer. After eight days of routine alkalis, no symptoms
27 R L	23	M	Nov 9, 1 m Nov 15, 1 m Nov 23, a m	7.16 7.15 7.15	65.5 71.1 71.9	575 525 588		13.4 15.7			Gastric ulcer. Routine alkalis, November 9 to November 23, mild symptoms of alkalosis began November 22
28 W W	44	M	Feb 28, p m	7.15	72.1	600	320	12.5	38.7		Duodenal ulcer. After six weeks of routine alkalis, no symptoms
29 F H	25	M	Mar 16, 1 m Mar 17, p m	7.19* 7.15*	66.4 71.1			11.9	38.7		Duodenal ulcer. Routine alkalis from March 9 to March 19, no symptoms
30 E W	39	F	Feb 11, a m	7.15	70.8	575					Duodenal ulcer. Routine alkalis for seven days, mild symptoms of alkalosis
31 F W	42	M	Mar 31, p m April 8, p m April 9, a m April 18, p m April 19, a m	7.11* 7.15* 7.39* 7.10* 7.34*	62.6 72.1 69.2 69.2 61.5	600		17.2 11.2	12.3 28.8		Duodenal ulcer. Routine alkalis from April 1 to April 19, moderate symptoms of alkalosis, after one week

32 H A	10	M	Jan 25, a m	7 15	62.6	588		15.2	95.3		Diodenal ulcer and gastric ulcer	No alkalis, vomiting, slight symptoms of alkalosis
33 J C	53	M	Jan 25, a m	7 15	60.7	600	115	12.3	25.6		Diodenal ulcer, moderate obstruction	January 25 after eight days of routine alkalis, mild symptoms of alkalosis, January 25 to Jan
			Feb 16, a m	7 10*	56.0	628	139	11.0	29.1		Diodenal ulcer	January 27, before gastro-enterostomy
34 M S	50	F	April 10, p m	7 13*	61.7	619					Diodenal ulcer	Calcium carbonate, 9.0 grains (23 Gm.), from April 11 to April 19, no symptoms of alkalosis
			April 11, a m	7 12*	61.1							
			April 18, p m	7 10*	61.5							
			April 19, a m	7 13*	62.0	594						
35 P S	47	M	June 16, 1925	7 13*	71.0			11.3			Diodenal ulcer, moderate obstruction	June 16, after ten days of routine alkalis, no symptoms, gastro-enterostomy, June 26
			June 30, 10.25	7 11*	59.0			11.0	27.0			
			July 13, 10.25	7 13*	57.0							
36 L P	35	M	Mar 9, a m	7 11	57.0	575	112	11.0	38.7		Diodenal ulcer	March 9, before alkalis, routine alkalis, March 9 to discharge, no symptoms
			Mar 16, a m	7 10*	63.3							
			Mar 25	7 15*	57.0	588		11.8	28.8			
37 P H	46	M	Dec 13, a m	7 11*	66.1	557	311	13.3	11.1		Diodenal ulcer	Routine alkalis, December 10 to December 15, no symptoms, gastro-enterostomy, December 20
			Dec 20, a m	7 13	66.2	575	301	11.3	35.3			
			Dec 31, a m	7 30*	67.3	570	111	13.9	12.1			
38 I I	33	F	Mar 29	7 10*	38.5	558		12.0	27.0		Diodenal ulcer	Routine alkalis, March 31 to April 2, moderate symptoms of alkalosis, no alkalis, April 2 to April 8, then enlarged magnesium, 50 grains (3.0 Gm.), and calcium carbonate, 1.0 grains (7.8 Gm.) daily, and less symptoms
			April 8, a m	7 10*	59.3							
			April 18, p m	7 10*	58.0							
			April 19, a m	7 11*	56.0	606						
39 C W	11	M	Mar 18, p m	7 11*	59.5	562	126	11.2	35.0		Diodenal ulcer	From March 19 to discharge, enlarged magnesium 50 grains (1.3 Gm.) and calcium carbonate, 150 grains (29 Gm.), no symptoms
			Mar 19, a m	7 10*	53.3	588	150	11.3	38.0			
			Mar 19, p m	7 11	61.7	581		12.3	35.0			
			Mar 31, a m	7 11	59.8							
			April 7, p m	57 11	61.7	563		13.0	12.2			
			April 8, a m	7 10	61.5							
40 P W	32	F	Feb 6, a m	7 10*	68.3	556	129				Diodenal ulcer	After six weeks of routine alkalis, no symptoms
41 L B	38	F	Jan 5, a m	7 39	59.8	545	310	11.1	40.1		Diodenal ulcer, marked obstruction	After five days of routine alkalis, moderate symptoms, only one kidney, phosphate and Moseenthal tests negative
42 W B	36	M	Jan 6, a m	7 39	59.8						Diodenal ulcer	alkali obstruction
					59.8	571	293	11.2	17.0		Diodenal ulcer	After seven days of routine alkalis, no symptoms
43 M W	33	F	Feb 11, p m	7 10*	66.1						Diodenal ulcer	After seven days of routine alkalis, no symptoms
			Mar 10, p m	7 11*	60.7	600	327	11.5	35.3			
			Mar 11, a m	7 12*	60.7	600	316	13.0	36.6			
44 M W	16	F	Feb 8, a m	7 38	45.7	613	313	11.0	28.5		Diodenal ulcer	After seven days on calcium carbonate, 60 grains (1.0 Gm.) and calcium carbonate, 100 grains (9 Gm.) until symptoms of alkalosis disappeared when alkalis were stopped
											Diodenal ulcer	After seven days of routine alkalis, no symptoms
45 L C	26	M	April 21, p m	7 11*	63.6						Diodenal ulcer, April 8, before alkalis	After ten days of alkalis, no symptoms
			April 22, a m	7 39*	62.6	576						
46 C H	25	M	April 2, a m	7 31*	56.9	588		15.3	32.3			
			April 18, p m	7 13*	71.1							
			April 19, a m	7 17*	64.3	600						

* Determination made colorimetrically

TABLE 1—Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Recovering Alkalosis, Including Observations on Several Miscellaneous Conditions—Continued

Case	Age	Sex	Date, 1925-1927	pH	Plasma		Hemo- globin, Gm	Non protein Nitro- gen, Mg	Ure- a Nitro- gen, Mg	Diagnosis, Comment
					Carbon Dioxide Con- tent, Cc	Chlorine as Sodium Chloride, Mg				
47 J H	51	M	Feb 26, a m	7.30	54.1	67	333	14.1	38.9	Carcinoma of stomach, pyloric obstruction Vomiting from 750 to 1,000 cc a day, no free acid
48 J N	71	M	Feb 5, a m	7.40	54.1	57	320	5.6	37.5	Carcinoma of stomach, slight obstruction at pylorus Irregular moderate vomiting
49 J Z	61	M	Feb 14, a m	7.43*	51.3	57	320	13.1	27.5	Carcinoma of stomach, obstruction at pylorus Moderate vomiting
50 P S	74	M	April 6, a m	7.49*	58.6	57	320	6.3	35.3	Carcinoma of stomach, obstruction Slight vomiting
51 H B	63	M	April 6, a m	7.43*	55.1	57	300	7.6	33.1	Carcinoma of stomach, obstruction Marked vomiting
52 H K	50	M	Nov 27, a m	7.48	59.8	57	312	12.2	45.5	Carcinoma of stomach, cardiac end Obstruction producing stricture
53 F R	52	M	Nov 27, 1 m Dec 1	7.47 7.45	55.1 59.8	57 57	311	12.1	41.1	Carcinoma of esophagus, producing nearly complete obstruction
54 O L	58	M	Nov 2, a m	7.46	57.0	60	355	12.5	41.1	General carcinomatosis Marked emaciation
55 A T	71	F	Nov 27, a m Dec 1 1 m	7.49 7.47	58.9 58.9	60 60	340	11.8	33.7	Secondary carcinoma of liver Jaundice the only symptom
56 J G	70	M	Jan 31, a m	7.41	57.9	57	300	5.6	35.3	Carcinoma of the colon Severe diarrhea
57 F K	32	M	Jan 31, a m	7.39	57.9	58	311	14.2	37.5	Ulcerative colitis Severe diarrhea, no other symptoms
58 C C	18	F	Feb 26, p m Mar 9 1 m	7.41	70.2 57.9	58 58	316	12.7	33.4	Nervous vomiting, on admission after 10 per cent dextrose and saline solution by rectum sodium bromide, 240 grains (15.6 Gm) daily, vomiting about stopped
59 I C	29	M	Oct 26, a m Nov 1, a m	7.44 7.38	64.7 63.4	61 60	315	14.5 11.5	12.1 10.4	Nervous vomiting headaches and drowsiness, relieved by dextrose and saline solution
60 J I	54	F	Mar 7, a m	7.43	77.3	54.2	358	11.6	29.6	Postdiphtheritic neuritis, vomiting, symptoms relieved by intravenous and rectal 10 per cent dextrose and physiologic sodium chloride solution
61 L C	56	F	Nov 13, a m	7.40	57.9	61.3	333	3.3	21.2	Paraneoplastic anemia No symptoms of alkalosis
62 L D	62	M	Jan 31, a m	7.43	56.0	530	300	7.2	41.4	Paraneoplastic anemia Drowsy vomiting
63 L D	23	M	Nov 3, a m Nov 9, a m Nov 16, a m Nov 27, 1 m	7.40 7.40 7.45 7.40	66.0 57.0 64.5 55.1	606 613 614 610	300 315	9.4 8.2 13.8	27.4 31.0 62.5	Chronic diffuse nephritis November 3, before medication Calcium carbonate, 640 grains (22 Gm) daily, from November 4 to November 27, no symptoms whatever, urine albumin, 2+ average 1,000 cc. by urine and granular casts, 1+ to 2+ average blood pressure, 100/90 slight edema
64 J S	53	M	Nov 12, a m	7.45	65.5	64.6	346	9.2	27.7	Chronic intestinal nephritis
65 L W	66	M	Nov 12, a m	7.38	43.8	61.3	313	5.6	89.0	Chronic intestinal nephritis, creatinine, 11.1 mg

* Determination made colorimetrically

Clinically, one of us (W E G) noted the symptoms and signs of alkalosis for a long time before he appreciated their significance or even suspected their cause. In a review of the end results in several hundred patients with peptic ulcer treated by the Sippy method¹⁹ it became evident that many discontinued the treatment shortly after leaving the hospital "because the powders made them sick." In our discussions with such patients, we have often felt that this was a matter of prejudice or distaste or only an inconvenience. Many such patients were considered neurotic and the headache, distaste for milk, subjective numbness and tingling of the hands and feet, aching of muscles and general "nervousness" were believed to be functional and independent of the treatment, even though the patients usually blamed the alkalis. In this study of individual patients under treatment we have been able to find, in at least a part of the cases, some changes in the blood which seem correlated with their clinical symptoms. We have also shown that these chemical changes could be produced by the alkalis and that the blood might become normal when the alkalis were stopped. In certain cases, there were other factors in addition to the powders which produced alkalemia. In some patients the intolerance to alkalis was only temporary, the disagreeable symptoms often disappearing without any change in the management. The study of the blood chemistry followed in a number of cases over several months, indicates that the alkalemia may decrease or disappear after a time. In some cases the symptoms of alkalosis appear early, even within the first twenty-four hours when alkalis are administered, as in the Sippy routine. More commonly the symptoms and the changes in the blood chemistry appear much more gradually and either appear or become most marked after a week or ten days of the alkali treatment. If the symptoms have not appeared within the first two weeks of this management, they are not likely to become manifest later. To avoid clinical alkalosis and other complications in the medical treatment of persons with peptic ulcer, it has seemed advisable to keep all patients receiving the large doses of alkali under close observation, preferably in the hospital for at least two weeks. After this trouble in management was experienced, certain patients, particularly those with obstruction who had previously refused surgical treatment, finally agreed to allow the performance of an operation.

It is not our purpose here to discuss the relative merits of medical treatment with and without alkalis. In general, the Sippy form of management¹⁹ was employed in the medical treatment of persons with peptic ulcer in this hospital. It is a widely used form of treatment.

¹⁹ Sippy, B W. Ulcer of the Stomach, Nelson's Loose Leaf Medicine 5: 238, 1920.

but we do not believe that many physicians give sufficiently large doses of alkali to neutralize completely the free acid in the stomach. In the series of cases which we have studied, a consistent effort has not been made to control the free acidity so completely. The general principles of the Sippy management have been employed, hourly feedings with alkali powders having been given midway between the feedings and for four, or in some cases, five doses after the last feeding. The dose of alkali powder has been what may be termed the average dose as outlined by Sippy in his publications. In perhaps half of the cases studied, the free acid was completely neutralized. Rarely has the amount of alkali given in twenty-four hours exceeded the average or routine dose. In a few cases, when aspiration tests did not show free acid in the gastric juice, the dose was decreased. When an increase in the amount of alkali was made it was rarely in the form of soda but, as recommended by Sippy, in the form of calcium carbonate. The average total daily dose of magnesium oxide was about 45 grams (3 Gm.), of calcium carbonate, 100 grams (6.6 Gm.), and of sodium bicarbonate, 310 grams (20.6 Gm.). This dosage applies to the average patient receiving what may be best termed the routine management. As indicated in the table, certain variations were tried with a number of these patients in an effort to study the effect on the blood chemistry produced by or attributable to sodium bicarbonate and to calcium carbonate. Magnesium oxide alone without any other alkali could not be used in any case in sufficient quantity to approximate the neutralizing effect of the combined alkalis, and therefore the effect, if any, produced by magnesium oxide alone could not be studied. Only an occasional patient could take as much as 70 grams (4.6 Gm.) of magnesium oxide without producing intestinal cramps or diarrhea. In ten patients the effects of magnesium oxide and calcium carbonate, without sodium bicarbonate, were studied. Whenever sodium bicarbonate was omitted, enough calcium carbonate was given to neutralize the equivalent of the soda.

In those cases reported by Jordan¹⁷ and also in those of Hardt and Rivers,¹ the patients were probably receiving on the average somewhat larger doses of alkali than the patients in our series, because an effort was made by them completely to neutralize the free hydrochloric acid, as was always recommended by Sippy.

In our study, especially in those patients showing symptoms of alkalosis, we have observed some changes in the blood chemistry and relief from symptoms when sodium bicarbonate was replaced by calcium carbonate. The only disagreeable result that we have ever noted clinically from the administration of calcium carbonate is the tendency to constipation with the formation of hard, dry and lumpy stools, a fecal impaction occasionally being produced. Recently, Loevenhart and Cran-

TABLE 2—Summary of Data on Patients with Peptic Ulcer Showing Disturbances of Acid-Base Balance

Case	Age	Location of Ulcer	Obstruction	Alkali Administration	Symptoms of Alkalosis	Date, 1926-1927	pH	Carbon Dioxide Content, per Cent by Volume, Chloride, Mg
1 G L	53	Duodenum	Marked	No alkalis	Marked	Jan 5, a m Jan 24, a m	7.6+ 7.34	129 71
2 C D	66	Duodenum	None	Routine alkalis	Mild	Nov 8, a m	7.55	79
3 R P	33	Duodenum	None	Routine alkalis	Marked	Dec 13, a m Mar 18, p m	7.51 7.50	82 78
4 D B	48	Duodenum	Slight	Routine alkalis	Marked	Feb 26, a m	7.53	74
5 O D	43	Duodenum	Slight	No alkalis Cultured magnesium and calcium carbonate only	Marked	April 22, p m	7.52	68
6 C S	30	Duodenum	Marked	Cultured magnesium and calcium carbonate only	None	Nov 19, a m Nov 23, a m	7.52 7.11	77 58
7 W W	67	Stomach	Slight	Routine alkalis	Mild	Nov 30, a m	7.52	73
8 F H	27	Duodenum	None	Routine alkalis	Marked	Nov 30, p m	7.52	78
9 A C	75	Stomach	Marked	Routine alkalis	None	April 21, p m	7.52	69
10 D H	70	Stomach	Marked	Routine alkalis	None	April 22, a m	7.46	62
11 A N	42	Stomach	None	Cultured magnesium and calcium carbonate only	Moderate	Nov 22, a m	7.51	61
12 L O	34	Duodenum	Marked	No alkalis	Moderate	Nov 22, a m	7.51	72
13 O J	34	Duodenum	None	Routine alkalis	None	Nov 22, a m	7.51	65
14 R P	20	Duodenum	None	No alkalis	Mild	April 1, p m	7.51	66
15 L J	39	Duodenum and stomach	None	Routine alkalis	None	Dec 16, i m	7.51	189
16 C R	55	Duodenum	None	Routine alkalis	None	Mar 8, p m	7.51	71
17 G S	54	Duodenum	Slight	Routine alkalis	None	Mar 25, p m	7.50	69
18 J H	41	Duodenum	None	Routine alkalis	None	Dec 2, a m	7.49	75
19 C P	25	Duodenum	None	Routine alkalis	None	Feb 11, p m	7.49	73
20 J J	27	Duodenum	None	Routine alkalis	None	Mar 11, p m	7.49	75
21 O P	34	Duodenum	Marked	Routine alkalis	None	Mar 30, p m	7.49	69
				Cultured magnesium and calcium carbonate only	None	Dec 13, a m	7.48	76
					None	April 11, p m	7.48	82
					Moderate	May 20, 1925	7.48	94

dall²⁰ have advocated calcium carbonate as the best antacid in the treatment of persons with peptic ulcer. From our study it seems evident that calcium carbonate is much less productive of alkalemia than sodium bicarbonate. It is obvious that if calcium carbonate and magnesium oxide are given in excess, this excess should not lead to the presence of free alkali, as in the case of sodium bicarbonate. Furthermore, the calcium chloride (and magnesium chloride) which is formed by the interaction with hydrochloric acid in the stomach is probably in a large measure reconverted to some insoluble form, such as the carbonate or phosphate, in the intestine and the chloride ion reabsorbed. At any rate, this is what might be expected from the observations of Haldane, Hill and Luck²¹ on the production of acidosis by the oral administration of calcium chloride.

CLINICAL SYMPTOMS AND VARIOUS CONDITIONS

The chief symptoms observed were headache, drowsiness, anorexia, nausea, vomiting, muscle-ache, nervousness and mental depression. Other less common nervous symptoms, such as a feeling of weakness and faintness, subjective "numbness" of the extremities, delirium, rapid and irregular respiration and marked irritability were also attributable to the alkalosis. The symptoms of nausea and vomiting occurring in patients with pyloric obstruction might be considered due to the obstruction and gastric irritability. When these symptoms paralleled other manifestations of alkalosis and increased with the administration of alkalis and with the alkalinity of the blood and subsided when the alkalis were stopped, it seemed likely that these gastric symptoms were at least in part due to the alkalosis. These symptoms occurred in some patients without obstruction when they did not exist before alkalis were given in large amounts. The muscle-ache was a fairly common symptom. Some complained of distress in the muscles of the back of the neck, or of pain in the calves of the legs and muscles of the arms, while others described the sensation as though their muscles were sore or as though they had an acute infection, such as influenza. Headache is a prominent and fairly constant symptom. In some instances, the headache was extreme and occurred in persons ordinarily not subject to headache. It was described by some as a feeling of great fulness and again, as if there were a band encircling the head. Drowsiness occurred as a well marked symptom in five patients and, at least in some instances seemed independent of weakness. At times these patients would arouse

20 Loevenhart, A. S., and Crandall, L. A. Calcium Carbonate in the Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, *J. A. M. A.* **88** 1557 (May 14) 1927.

21 Haldane, J. B. S., Hill, R., and Luck, J. M. Calcium Chloride Acidosis. *J. Physiol.* **57** 301, 1922-1923.

when addressed but would fall asleep at once, even before we left the bedside. They had to be aroused for food and medication. In the past, less well defined symptoms of "nervousness," depression, a feeling of marked weakness, tingling and "numb-feeling" in the extremities have been considered as functional and not attributable to any physical change in the patient. More careful observation convinces us that often these symptoms are directly due to alkalosis. After a few days they may disappear spontaneously.

Age—As observed by Venables,¹¹ age seems to be a significant factor in the incidence of alkalosis in patients receiving alkalis. Definite symptoms as well as the changes that occur in the blood in alkalosis were observed in thirteen patients with ulcers. Their ages ranged between 33 and 75 years. Two were aged 36 and one, 33. The most marked symptoms occurred in a man, aged 53. He had a marked pyloric obstruction from a duodenal ulcer, but did not receive alkalis. The next most striking example of this phenomenon was seen in a man, aged 33, who had a duodenal ulcer that did not produce obstruction but who received alkalis that contained relatively large amounts of sodium bicarbonate. Neither of these patients had any recognizable renal damage. The younger of the two patients was so ill that on several occasions the alkalis had to be stopped altogether, but there would be a return of gastric distress when the alkalis were stopped and he refused operation. The older patient was treated surgically as soon as his general condition permitted. The average age of these thirteen patients presenting symptoms of alkalosis was 53 years. Four were women and nine were men. The average age of the entire group in this study was 40 years. Nine were women and thirty-seven were men.

Obstruction—Well marked obstruction was present in six of the patients with typical symptoms of alkalosis. These patients usually received by rectal administration all of the 5 or 10 per cent dextrose in physiologic sodium chloride solution that they could retain and often several intravenous injections of this solution, especially when they were being prepared for operation. This treatment, no doubt had considerable influence on the severity of their symptoms and the degree of alkalemia.

Nephritis—Definite nephritis was not recognized in any of the patients who later developed alkalosis. Linder²² pointed out that when considerable renal insufficiency is present, there is evidence of failure to adjust the acid-base balance with the customary delicacy. It has been known for some time that persons with an advanced form of chronic

22 Linder G. C. The Effect of Mineral Acid on Acid-Base Regulation in Health and Nephritis, *Quart J Med* 20 285 (April) 1927

interstitial nephritis invariably suffer from an acidosis²³ We did not see any evidence of renal damage resulting from the use of the alkalis in this series of cases One patient, a woman, aged 48, had a slight hematuria for a day or two at a time when she also had symptoms of alkalosis, but there was no other evidence in the urine or in the blood chemistry of renal damage In one patient in whom a nephrectomy had been performed five years before our observation, evidence of renal insufficiency was not found at any time In a considerable number of cases, routine determinations of phenolsulphonphthalein were made, all of which were normal Frequent chemical and microscopic examinations of the urine did not show evidence of nephritis There were slight elevations in nonprotein nitrogen in the blood, but none of the cases studied showed any marked retention

One patient, case 63 in the miscellaneous group at the end of table 1, who did not have an ulcer or any other gastro-intestinal condition but who was under treatment for a chronic diffuse nephritis, was given calcium carbonate in large doses for several days, chiefly to determine if in this person with a well defined nephritis an alkalosis would result A change was not produced in the renal efficiency, at least during our period of observation He did not suffer any inconvenience and we did not note any change in his general condition The protein intake was restricted to 40 Gm and the diet was "salt-free" He had slight edema both before the administration of the calcium carbonate and while receiving it, and there was no appreciable variation in the edema or in the fluid output

Tetany—In none of our patients was tetany observed At times when handling patients with marked obstruction and intense vomiting, we have noted this phenomenon but have not made a study of the blood chemistry in such cases as in the group here described The occurrence of tetany in patients with alkalosis has been discussed by McVicar¹³ and in the reports from Guy's Hospital by Hurst, Houghton, Venables and Lloyd¹⁴

The Appearance of Symptoms—We were interested in seeing how quickly the effects of the alkalis on the blood might appear and disappear In some instances the first symptoms, usually headache and anorexia, appeared as early as the third day of alkali therapy Less definite evidence of alkalosis, accompanied by a fairly definite alkalemia, may occasionally occur on the first day Usually the well defined symptoms of alkalosis did not appear until from the sixth to the eighth day Often the milder symptoms disappeared entirely without any change in the treatment It was noted that when symptoms did occur they

23 Chace, A F, and Myers, V C Acidosis in Nephritis, J A M A 74 641 (March 6) 1920

TABLE 3—Data on Patients Showing Alkalosis of the Late Afternoon

Case	Age	Uter	Obstruction	Alkalis			Symptoms	Date, 1926	Time	Carbon Dioxide Content, per Cent by Volume	Plasma Chloride as Sodium Chloride, Mg
				Calcium Magnesia	Calcium Carbonate	Sodium Bicarbonate					
3 R P	41	Duodenal	None	50 gralms (1.2 Gm)	80 gralms (6.2 Gm)	200 gralms (10 Gm)	Marked	Feb 11, 5 10 p m	7 56	75	563
				20 gralms (1.1 Gm)	280 gralms (18.5 Gm)	0	None	Feb 11, 8 15 a m	7 13	50	591
								Mar 18, 5 00 p m	7 50	58	650
								Mar 19, 9 30 a m	7 30	54	609
1 D H	45	Duodenal	Slight	30 gralms (1.0 Gm)	110 gralms (7 Gm)	360 gralms (23.3 Gm)	None	April 27, 5 00 p m	7 52	68	556
								April 28, 7 00 a m	7 46	61	
6 C S	30	Duodenal	Marked	20 gralms (1.1 Gm)	600 gralms (39 Gm)	0	None	Nov 30, 6 15 a m	7 52	73	585
								Nov 30, 6 45 p m	7 49	72	
8 L H	27	Duodenal	None	30 gralms (1.0 Gm)	110 gralms (7 Gm)	360 gralms (23.3 Gm)	None	April 21, 1 50 p m	7 52	69	
								April 28, 7 10 a m	7 46	65	613
13 O J	41	Duodenal	None	20 gralms (1.1 Gm)	140 gralms (5.1 Gm)	110 gralms (20.6 Gm)	None	Mar 5, 6 40 a m	7 45	68	540
								Mar 5, 6 10 p m	7 31	71	
16 C R	55	Duodenal	None	70 gralms (1.5 Gm)	80 gralms (5.2 Gm)	310 gralms (20 Gm)	None	Feb 11, 8 50 a m	7 41	66	600
								Feb 11, 6 30 p m	7 51	73	550
17 G S	51	Duodenal	Slight	70 gralms (1.5 Gm)	80 gralms (5.2 Gm)	100 gralms (20 Gm)	None	Mar 11, 6 20 a m	7 6	64	595
								Mar 11, 6 30 p m	7 49	75	605
20 L H	46	Duodenal	None	50 gralms (3.2 Gm)	60 gralms (3.9 Gm)	240 gralms (11.9 Gm)	Marked	Feb 21, 6 30 p m	7 46	78	
								Feb 21, 6 10 p m	7 39	66	
7 W W	67	Gastro	Slight	60 gralms (3.0 Gm)	70 gralms (4.5 Gm)	270 gralms (17.6 Gm)	Quite marked	Nov 30, 6 30 a m	7 0	68	540
								Nov 30, 6 30 p m	7 12	78	515

increased during the day when alkalis were administered. The patients who had severe headache might feel well in the morning but by 3 or 4 o'clock in the afternoon would have a raging headache. When the treatment was continued, this might be a daily occurrence. The blood became more alkaline at the end of the day when the routine determinations of alkali were being taken and as a rule returned to a more normal condition in the morning before the administration of the alkalis was resumed (table 3).

LABORATORY AND CLINICAL STUDY

The analyses of the blood included estimations of the p_{H} , both colorimetrically and electrometrically, the carbon dioxide content, the plasma chloride, the serum sodium and the inorganic phosphorus of the serum or plasma, in addition to such more or less routine analyses as those of the hemoglobin, nonprotein and urea nitrogen, uric acid, creatinine and sugar. For the determination of the p_{H} , carbon dioxide content and chlorides, oxalated plasma separated under oil was employed. Electrometric determinations of the p_{H} were carried out at 38 C and the colorimetric determinations at room temperature and corrected to 38 C. The technic employed for these determinations has been briefly described elsewhere by Myers and Muntwyle.²⁴ The Van Slyke-Stadie²⁵ method was employed for the carbon dioxide, the Myers-Short²⁶ method for the chlorides and the Kramer-Tisdall²⁷ method for the sodium. (Although we were able to obtain quantitative recoveries with added sodium, our results appear to be a little low. It is believed, however, that they are comparable.) As a routine, all of the blood specimens were taken in the early morning (from 6 to 7 a. m.) before food or alkali had been given, obviously at a time unfavorable for the detection of a mild alkalemia. As has been pointed out by some authors, there are likely to be minor changes in the blood reaction after the ingestion of a meal, as hydrochloric acid is secreted in considerable quantity into the stomach. In persons with obstruction or marked hypersecretion, this accumulation of acid in the stomach and consequent shift of acid-base equilibrium may be independent of the administration of alkalis. In order to bring out the influence of alkali

24 Myers, V. C., and Muntwyle, E. The Colorimetric Estimation of the Hydrogen Ion Concentration of Blood, *J Biol Chem* **78** 243 (June) 1928.

25 Van Slyke, D. D., and Stadie, W. C. The Determination of the Gases of the Blood, *J Biol Chem* **49** 1, 1921.

26 Myers, V. C., and Short, J. J. The Estimation of Chlorides in Blood, *J Biol Chem* **44** 47 (Oct.) 1920.

27 Kramer, B., and Tisdall, F. F. A Simple Method for the Direct Quantitative Determination of Sodium in Small Amounts of Serum, *J Biol Chem* **46** 467, 1921.

administered during the day, the blood specimens were again taken in the late afternoon or early evening in some cases. In most of the cases studied, determinations were made before any alkalis were administered and again after a week or more of treatment with alkalis.

About two thirds of the patients with ulcer studied at some time showed either a high bicarbonate value or p_H or both. Of these, twenty-one cases (out of the total of forty-six cases) showed an uncompensated alkalosis, if electrometric p_H values of 7.48 or above may be taken as a reliable guide. Some of the more pertinent figures in these cases are summarized in table 2. Four of the twenty-one cases (3, 9, 11 and 12) with high p_H values gave normal figures for carbon dioxide content (from 58 to 66 per cent by volume), and might have been missed, if the determination of p_H had been omitted. Seventeen of the patients (table 1) with carbon dioxide contents ranging from 68.3 to 94.0 per cent by volume gave p_H readings ranging from 7.39 to 7.46 and therefore at the time of these determinations belonged to the compensated variety of alkalosis.

It has been recognized for some time that with the marked rise in blood bicarbonate in "high up" intestinal obstruction there is a corresponding fall in the plasma chloride. Jordan¹⁵ called attention to a similar change after the administration of sodium bicarbonate. This change stands out strikingly in our series of cases. A group of ten unselected patients with high figures for carbon dioxide content give an average plasma chloride of 558 mg. per hundred cubic centimeters as compared with an average of 591 mg. from fifteen analyses made in persons with normal carbon dioxide content, a difference of 33 mg. It is of further interest that the patients with high figures for the carbon dioxide content but low plasma chloride showed an average of 327 mg. of sodium per hundred cubic centimeters of serum, compared with 311 mg. for the other series of cases.

Clinically, as has often been observed by others, we noted the disagreeable symptoms of alkalosis most commonly when the plasma chloride was low and saw a marked improvement in the general condition of the patient when sodium chloride was administered, especially by the intravenous route. This procedure should be employed as a routine in the preparation of patients with pyloric obstruction for operation.

Somewhat less than half of the patients exhibiting an alkalemia of either the compensated or uncompensated variety showed a slight elevation in the nonprotein or urea nitrogen. There did not appear to be any relationship between this and the severity of the alkalosis, however.

Eight patients (cases 1, 6, 7, 15, 21, 33, 35 and 37 in table 1) with pyloric obstruction were studied before and after operation. In general patients with pyloric obstruction, especially if it is of high grade, are

transferred promptly to surgical treatment if they will consent to operation. Before operation they are prepared in accordance with the principles outlined by Berkman²⁸. In several of these patients with obstruction, operation was absolutely refused and it was necessary to treat them medically. In most of those patients with obstruction and well marked alkalosis before operation, the blood chemistry became essentially normal after removal of the obstruction. In the patient with pyloric obstruction who is either vomiting large amounts or is having frequent aspiration and gastric lavage, the loss of large quantities of acid in the gastric juice and the failure of adequate amounts of chloride to reach the small bowel lead to alkalosis. The administration of alkalis, particularly sodium bicarbonate, to such patients, as is frequently done if they have the characteristic ulcer pain, further increases the alkalosis. There is little doubt that soda should be withheld from these patients, and that either calcium carbonate or magnesium oxide or combinations of these two alkalis may be given with much greater safety. As an essential part of their treatment water and salt must be supplied either by rectum or, if necessary, intravenously or subcutaneously. In some of these patients who are dehydrated and who have alkalosis, unusual skill and effort are necessary to supply these two simple but important substances, water and salt. The veins are often so collapsed that the ordinary injections are difficult. The dextrose added to the solution is probably of considerable value in supporting the strength of the patient. In the postoperative period much may be done to save the life of such patients by continuing to supply an abundance of water and salt.

Gamble and McIver²⁹ indicated that the content of chloride in gastric juice is fairly constant and approximates that of the blood plasma. If the gastric juice vomited by the patient with pyloric obstruction contains this concentration of chloride, it is readily seen that the depletion of the plasma chlorides is rapid when a liter or two of the juice is being vomited each day. Ramos and Fox³⁰ directed attention to the rôle of water in maintaining the acid-base equilibrium and considered that dehydration promotes acidosis. Koehler¹⁶ and others discussed the effect of starvation in producing acidosis. It seems that some of these factors, in patients with obstruction and vomiting, counteract others. The effect of dehydration and starvation may in part reduce the alkalosis. The determinations concerning the blood chemistry only serve as a partial indication of the resulting balance, or imbalance.

28 Berkman, D. M. Preoperative Management in Cases of Gastric Retention, *M. Clin. N. Amer.* **5** 411 (Sept.) 1921.

29 Gamble, J. L., and McIver, M. A. Fixed Base in Gastric Juice, *Proc. Soc. Exper. Biol. & Med.* **23** 439, 1926.

30 Ramos, S., and Fox, G. L. Rôle de l'eau dans le maintien de l'équilibre acido-basique du sang, *J. de physiol. et de path. gen.* **24** 231 (April) 1926.

REPORT OF CASES

CASE 1—G L, aged 53 years, admitted to the hospital, Dec 27, 1926 had the typical symptoms and roentgen-ray evidence of a chronic duodenal ulcer producing almost complete obstruction. He had vomited large quantities of watery material for about ten days and had rapidly become weak. In the past two months he had lost about 25 pounds (11.3 Kg). In addition to the usual acid type of distress and unusual gastric hyperperistalsis, of which he was conscious, he complained of marked thirst, dryness of the mouth, and at the same time nausea, anorexia and vomiting independent of the abdominal discomfort. He volunteered the complaint of a steady dull headache which had been present for several days, and mentioned that his muscles were sore, "as if he had been pounded." He was noticeably apathetic and drowsy. He was vomiting several times a day, and the balance indicated that the quantity of vomitus was greater than his total fluid intake. The urine was scanty and contained a bare trace of albumin and a few hyaline casts. At times a single emesis would amount to between 1,000 and 1,500 cc. In two specimens of vomitus, the free acid was 30 and 27 and the total acid, 45 and 52. It was difficult to puncture a vein either to obtain blood for examination or to give intravenous salt solution. The blood specimen obtained on Jan 5, 1927, which was a few days after his most critical period, gave the highest p_H value that we have noted at any time in this entire study. The value of 7.6 "plus" is assigned, as the specimen exceeded even that figure in alkalinity, a standard not being immediately available to compare with this surprisingly alkaline blood. The carbon dioxide content of the plasma was also extraordinary, 120 cc per hundred cubic centimeters of plasma. The specimen was too small to determine the p_H electrometrically or to make the other routine determinations.

This patient had not received alkalis for some time before admission and none after admission to the hospital. He was given by rectum all of the normal salt solution containing 5 per cent dextrose that he could retain, twice, he was given about 800 cc of physiologic sodium chloride solution intravenously and smaller amounts subcutaneously. The stomach was washed out each night. It was impossible for us to get satisfactory specimens of blood again before operation. He was sufficiently improved so that gastro-enterostomy was performed on Jan 12, 1927. He had been stuporous, almost comatose, and evidently near death for a number of days and after the operation his condition was not satisfactory for ten days but by January 24, he was decidedly improved. The carbon dioxide content of the plasma was then 71.1 cc and the plasma chlorides, 0.55 per cent. The patient made a complete recovery.

CASE 6—C S, a negro, aged 30 years, with symptoms of a duodenal ulcer and roentgen-ray evidence of duodenal deformity, had been admitted to the medical service and after three weeks of instruction in the use of the Sippy management had been discharged with directions to continue the treatment. His monthly reports indicated that he was not getting along well. At his first admission there was no evidence of obstruction. He returned six months later with vomiting, visible peristalsis and evidence of obstruction. He vomited large amounts of gastric juice, and retained food, but only infrequently. During this second admission, while he was in the medical department prior to operation, the stomach was aspirated and washed each night, from 500 to 2,000 cc being obtained, the average amounting to about 1,100 cc. He was not given alkalis for ten days and on Nov 26, 1926 (table 1), was placed on magnesium oxide and calcium carbonate, without any sodium bicarbonate. The average total daily dose was 20 grams (13 Gm) of magnesium oxide and 600 grains (39 Gm) of calcium

carbonate The alkalis were discontinued four days before operation, and the usual preoperative measures for increasing the supply of salt and water were employed For more than a month he had refused operation but finally consented, and a gastro-enterostomy was done on December 14 He made an uneventful recovery Seventeen days after operation, the blood was normal At no time were there any definite symptoms of alkalosis Although the analyses of the blood indicated moderate alkalemia and some chloride deficit, his condition was not materially altered by the use of the alkalis when soda was excluded The removal of the obstruction relieved the alkalemia

CASE 21—O P, a woman, aged 34 years, presented the clinical picture of a duodenal ulcer with marked obstruction By vomiting and aspiration of the stomach, she was losing from 650 to 3,000 cc of gastric content daily, on the average, about 1,500 cc She complained some of headache, nervousness and muscle-ache in addition to anorexia, nausea and vomiting While we waited for her consent to operation, the treatment was chiefly the furnishing of physiologic sodium chloride solution by bowel, aspiration and lavage of the stomach each night, and a soft diet three times a day For two days only she received alkalis, about 75 grains (4.9 Gm) of magnesium oxide and 150 grains (10 Gm) of calcium carbonate, without soda On account of the recognized alkalosis, these were used only for the two days The analyses in the table indicate the marked alkalemia and low blood chloride content, due to the obstruction and vomiting rather than to the alkalis The change in the blood chemistry after the removal of the obstruction is remarkable

CASE 7—W B W, a man, aged 67 years, was admitted to the hospital with a diagnosis of gastric ulcer with slight obstruction He had lost considerable weight and had vomited moderately He was advised to have surgical treatment but did not accept this advice for several days He was placed on hourly feedings but without alkalis at first At this time, definite symptoms attributable to alkalosis were not present Because of severe distress he was placed on the routine alkalis on Nov 25, 1926, and these were continued until Dec 5, two days before operation He received on the average about 50 grains (3.3 Gm) of heavy magnesium oxide, 270 grains (17.6 Gm) of sodium bicarbonate and 70 grains (4.6 Gm) of calcium carbonate a day On November 29, four days after the alkalis were started he began to complain of headache and muscle-ache and on the fifth day there were pronounced symptoms of alkalosis with anorexia, nausea, vomiting, muscle-ache, apathy and marked drowsiness On this date the blood chemistry showed a marked change rather directly attributable to the alkalis The blood had been essentially normal five days before, or at the time the use of alkalis was started, and now there were pronounced alkalemia, a considerable increase in the carbon dioxide content of the plasma, especially at the end of the day, and a marked fall in the plasma chlorides On account of the pain this patient continued to receive alkalis, though somewhat less sodium bicarbonate, until he consented to have the operation In general, we have noted that there is more satisfactory relief from pain when soda is used than is secured from the other alkalis

Because we believed that sodium bicarbonate contributed more to the production of alkalemia than the other alkalis used in the Sippy treatment, we made some effort to determine the effects of the alkalis when soda was omitted Clinically, some of those patients who complained while they were being given the routine alkalis became com-

fortable when the soda was replaced by an equivalent of the other alkalis. Some of the patients were given only magnesium oxide and calcium carbonate for a control period and then for about a week were placed on the routine alkalis containing the sodium bicarbonate. Analyses of the blood were made at the beginning and end of this period. In some of these patients although an appreciable alkalemia developed after soda was given disagreeable symptoms attributable to alkalosis did not occur. In other patients this change in the alkalis produced the usual symptoms of alkalosis (cases 3 4 5 9 17 22 34 and 39 in table 1)

CASE 3—R. P. with an uncomplicated duodenal ulcer, began to have symptoms attributable to the alkalis after he had followed the routine (including sodium bicarbonate) for three days. He complained of a dull, steady headache at first although he could scarcely recall having had a headache before. He complained of nervousness and difficulty in remaining quiet in bed and stated that everything and everybody annoyed him. His muscles ached as if he were coming down with influenza. He developed a distaste for milk and cream and for other articles of soft diet. He preferred to be left alone and wanted the treatment stopped in the midafternoon. In the mornings he would feel better and practically free from the headache. Each day these symptoms seemed to grow worse. He questioned the benefits to be derived from such treatment. Finally the alkalis were temporarily discontinued and he felt all right. He was discharged from the hospital on alkalis but without any sodium bicarbonate. At the end of six weeks he was again placed on the routine alkalis (including sodium bicarbonate) and again had the same train of symptoms the headache being the most troublesome. The blood chemistry determinations of February 11 and 12 indicate a fairly severe alkalosis as the cause of these symptoms. It seemed of especial interest to note that the alkalemia was less in the morning at the time when his symptoms were least marked. The average daily dose of the alkalis while he was on the routine treatment was 50 grains (3.3 Gm.) of magnesium oxide 80 grains (5.2 Gm.) of calcium carbonate and 290 grains (19 Gm.) of sodium bicarbonate. When the soda was omitted he received as the average daily dose 20 grains of magnesium oxide and 280 grains (18 Gm.) of calcium carbonate and this represents a 10 per cent greater neutralizing value. This patient has continued the management without soda for five months and has not had further trouble.

CASE 22—L. H. a man aged 35 years with an uncomplicated duodenal ulcer did not have symptoms of alkalosis until he was placed on powders containing sodium bicarbonate. On February 8 before he took any alkalis his blood chemistry was essentially normal. From February 10 to the 17 inclusive he took as the average daily dose 50 grains (3.3 Gm.) of magnesium oxide and 120 grains (7.8 Gm.) of calcium carbonate. During this period the only important change noted in the blood chemistry was the fall in the plasma chlorides. On February 18 he began to take soda the average daily dose of alkalis in the next three days being 50 grains (3.3 Gm.) of magnesium oxide 60 grains (3.9 Gm.) of calcium carbonate and 230 grains (15 Gm.) of sodium bicarbonate. The neutralizing value of this combination is about the equivalent of 80 grains (5.2 Gm.) of soda more than the previous dosage. At 4 o'clock on the first afternoon that soda was given he began to have severe headache and this continued each day until the soda was stopped, the headache was less intense in the morning but increased

in the late afternoon. The urine on the third day of this treatment had a p_H of 7.85 at noon, of 7.90 at 3 p. m. and of 7.95 at 6 p. m. This patient was discharged on alkalis not containing sodium bicarbonate and he has not had a return of alkalosis.

Previous to making the study of the blood chemistry in this group of cases, one of us (W. E. G.) noted that patients might feel well in the morning but might complain of distaste for the milk, nausea, headache, drowsiness and general dislike of the management by the middle or latter part of the afternoon. Some patients would omit the last two or three hours of their management. We attributed this to a number of different things—distaste for the powders, dislike for the milk, souring of the milk (although the nurses and other patients assured us that the milk was sweet) or, finally, to lack of cooperation on the part of these patients. In this study we have seen some interesting changes in the blood chemistry between morning and night, when alkalis were given, and between night and morning as the patient excreted, the excess of alkali tending to restore the acid-base equilibrium to normal.

This is well illustrated by the data summarized in table 3. It will be noted that the p_H and carbon dioxide content are always higher and the plasma chloride lower in the evening than in the previous or following morning, the only exceptions being patients in whom the alkalosis was severe. In such instances, the time interval does not appear to be great enough to allow compensation.

In a few instances, not recorded, the p_H of the urine was followed but in all of these cases the kidneys were apparently readily able to excrete alkali. As pointed out by Myers and Booher,³¹ patients whose kidneys do not readily secrete an alkaline urine tolerate alkalis poorly.

ACID-BASE BALANCE IN SOME MISCELLANEOUS CONDITIONS

The study of the blood chemistry has been somewhat extended to include other conditions which to us seem related.

The first group to which we wish to call attention, the patients in cases 47 to 52, were all suffering from carcinoma of the stomach. None of these patients had symptoms of alkalosis. In two instances, cases 50 and 52, there was alkalemia, as indicated by the determinations of p_H . In all of these six patients, the carbon dioxide content of the plasma was normal or subnormal and in all in whom the plasma chlorides were determined there was a chloride deficit. In three patients with considerable secondary anemia, as indicated by the low hemoglobin content of the venous blood, a deficient oxygen carrying power of the blood may have had something to do with the carbon dioxide content and reaction of the plasma.

In patients with carcinoma of the stomach, there are a number of factors which disturb the blood chemistry. When obstruction is present at the cardiac

³¹ Myers, V. C., and Booher, L. E. Observations on the Excretion of an Acid Urine in Alkalosis, *Proc. Soc. Exper. Biol. & Med.* **22**: 513, 1925.

end of the stomach or in the esophagus, probably the chief factor is the failure to ingest sufficient water, food and salt so that eventually there is a chloride deficit and a tendency to acidosis. With an obstruction at the pylorus there is the additional factor of the loss of water and secretions from the stomach itself. Some patients, in whom the gastric juice has remained fairly normal with large quantities of free acid in the stomach, may present the same general picture as that of a benign ulcer at the pylorus with obstruction. The patient in case 10 during life was supposed to have had a carcinoma of the stomach with pyloric obstruction and the condition was thought inoperable. Postmortem examination revealed a large ulcer which had perforated at some time, probably months before our examination, the floor of the ulcer being formed by the anterior surface of the pancreas. On account of the patient's age, the extent of the pathologic change and the poor general condition, it is doubtful if surgical treatment would have offered him much benefit. However, in our review of this case, we realize that we should have employed the administration of physiologic sodium chloride solution and water more diligently.

Although the gastric juice of patients with carcinoma of the stomach often contains little if any free acid, there is reason to believe that the chloride content of this juice is nearly normal. Vomiting of large quantities of gastric juice by these patients may result in a depletion of the plasma chloride, though it is less productive of alkalemia than in those patients with peptic ulcer in whom the acid values are normal or increased.

Cases 52 and 53 are much alike in our consideration, because the blood chemistry is probably altered chiefly by the restricted intake and the resulting starvation and dehydration.

Cases 54 and 55 are tabulated for comparison with the other cases of carcinoma. The patients had late and rather generalized carcinomatosis without any recognized involvement of the digestive tube. Naturally their food and fluid intake was somewhat abnormal.

The patients in cases 56 and 57 who show little change in the elements of the blood which we studied, except a fall in the plasma chlorides, had severe diarrhea. Because they were severely ill their food intake was less than normal. The fluid intake was above normal, but the loss was sufficient to produce some dehydration.

Cases 58, 59 and 60 are grouped together because none of these patients had any evidence of organic disease of the gastro-intestinal tract nor disturbance of the gastric secretions. At the time of admission, only the carbon dioxide determination was made in case 58. We believe that the p_{H} was probably high at that time and that the plasma chlorides were much lower than when determined about two weeks later after the girl had been treated. Her history indicated that she had vomited "almost everything" for weeks before admission. Because of her obvious neurosis, we did not know how many of her symptoms and complaints were due to the general nervous condition and how many were due to an alkalosis resulting from the prolonged vomiting or regurgitations. In case 60 the vomiting occurred almost immediately after any food or drink was taken and the patient became extremely emaciated. We had a great deal of difficulty in supplying adequate nourishment and fluids but ultimately succeeded in getting her up and about.

The patients in cases 61 and 62 vomited a great deal in the terminal stages of pernicious anemia. It would be difficult to tell how many of their symptoms were due to the nervous manifestations of the disease and failing strength and how many were due to the vomiting. So far as we know the actual chloride

content of the gastric juice in such cases has not been determined. The absence of free acidity would probably lessen the tendency to alkalosis when severe vomiting occurs in such cases, and there are factors which would tend to produce acidosis.

The patients in cases 63, 64 and 65 had chronic nephritis. The patient in case 63, previously mentioned, received larger doses of calcium carbonate than would ordinarily be administered to control gastric acidity. Our purpose was to note any untoward effects produced by the calcium carbonate in a patient who was known already to have advanced nephritis. We did not note any disagreeable effects. There was no apparent disturbance of the acid-base equilibrium. We obtained normal or slightly elevated values for the plasma chlorides, which may have depended on the diffuse or mixed nephritis. We did not feel justified in repeating this test with the substitution of sodium bicarbonate for the calcium carbonate. The nephritis was of the chronic interstitial type in both case 64 and case 65, and neither of these patients received alkalis.

Naturally, we cannot establish many facts from this small group of miscellaneous cases but mention them because of their similarity to certain cases of peptic ulcer complicated by vomiting, obstruction, anemia and nephritis.

CONCLUSIONS

A series of forty-six patients with gastric or duodenal ulcer has been studied, with particular reference to the acid-base balance. A definite correlation between the alkalemia in these cases and a group of clinical symptoms that are chiefly nervous in character has been observed. About two thirds of these patients at some time showed a high carbon dioxide content or p_{H_2} or both, and twenty-one showed an uncompensated alkalosis, if electrometric p_{H_2} values of 7.48 or above may be taken as a reliable guide. Pyloric obstruction is obviously an important factor in the production of alkalosis. The surgical relief of the pyloric obstruction restores the acid-base balance and the chloride deficit in these cases.

When used in such amounts as are commonly employed in the treatment of peptic ulcer by the Sippy method, the alkalis almost always produce characteristic changes in the blood chemistry, even though the symptoms of alkalosis may not occur. When calcium carbonate and magnesium oxide are employed without the use of soda in this management, alkalemia is decidedly less severe and the clinical symptoms of alkalosis are unlikely to appear, especially if the complication of obstruction or vomiting does not occur. The changes produced by the alkalis are most marked at the end of the day, and during the night the condition tends to return to normal.

In this limited series of cases, there was no definite evidence that the alkalemia in the degree observed by us was productive of any renal damage.

With the rise in the blood bicarbonate, there is a corresponding fall in the plasma chlorides. The rise in the bicarbonate appears to be accompanied in many cases by a slight rise in the serum sodium.

The clinical symptoms of alkalosis are again briefly described. Many of the symptoms which have previously been considered as functional are due to a disturbance in the nervous system secondary to the alkalemia.

The importance of administering water and sodium chloride to patients suffering from alkalosis and especially as a preoperative and postoperative measure seems obvious but is again emphasized. When patients who have been receiving alkalis as a part of the treatment for ulcer consent to operation, the alkalis should be omitted for at least several days before the operation. During this interval, the usual methods of forcing water and salt should be employed.

A miscellaneous group of nineteen cases has been discussed in connection with the alkalosis occurring in the treatment of persons with peptic ulcer because some of these conditions have similar features producing changes in the blood chemistry. The number of cases in any particular group was insufficient to warrant any general conclusions concerning the blood chemistry of such a group as a whole.

TOTAL CHLORIDE CONCENTRATION AND ACIDITY OF THE GASTRIC CONTENTS

A COMPARATIVE STUDY *

F D GORHAM, M D

C MALONE STROUD, M D

AND

MAITLAND HUFFMAN, M D

ST LOUIS

Various procedures have been recommended for measuring gastric secretion in man. Certain English investigators¹ have suggested that the total chlorides of a sample of contents of the stomach as determined by the direct Volhard method, after filtration but without ashing, is more accurate than the acidity as an index to the amount of gastric secretion, because much or little of the acid secreted may have been neutralized. They state further that a comparison of the acidity, as determined by the Toepfer method, and the total chlorides gives information as to the amount of neutralization that has occurred. However, this depends on the hypothesis that the chief source of the chlorides in the stomach is hydrochloric acid, an assumption of fundamental importance and one worthy of investigation.

In this paper, we report the results of a comparative study of the total chloride concentration and acidity of the gastric contents in a series of cases presenting both normal and abnormal conditions.²

METHOD OF PROCEDURE

The morning after a night's fast, the contents of the stomach were aspirated. The subjects were then given one of two test meals. At first a shredded wheat biscuit and 400 cc of tap water containing 6 mg of phenol-sulphonphthalein were used, but owing to the fact that such a test meal was

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1 Baird, M M, and Campbell, J M H. The Importance of Estimating Chlorides in the Fractional Test Meal Samples, and Some Experiments with the Duodenal Tube, *Guy's Hosp Rep* **74** 40, 1924. Bolton, Charles, and Goodheart, G W. Duodenal Regurgitation Into the Stomach During Gastric Digestion, *Lancet* **1** 420, 1922.

2 We report results only from a representative number of the many subjects studied. Specimens containing excessive amounts of mucous or bile are not included. Patients with gastric carcinoma are also excluded, due to the frequent presence of blood in the gastric contents.

found to contain variable amounts of chlorides, a second test meal consisting of 400 cc of distilled water containing 6 mg of phenolsulphonphthalein was employed. At a definite period (45 minutes) after the test meal, the stomach was emptied as completely as possible. In certain cases on successive days, after removal of the contents of the stomach during fasting, test meals were given and the contents of the stomach removed at 30, 60, 90 and 120 minutes, respectively, after the test meal.

A comparative study was made of the free hydrochloric acid, total acidity and total chlorides of the contents during fasting and a similar study of the phenolsulphonphthalein concentration, the free hydrochloric acid, total acidity and total chlorides in a sample of the mixed chyme after the test meal. The presence of excess mucus and the presence or absence of bile were recorded. The free acid and total acidity were estimated according to the Toepfer method. The chlorides were determined by the direct Volhard procedure. To make comparison easy the chlorides reckoned as sodium chloride are expressed as tenth-normal hydrochloric acid.³

The factor of "test meal dilution"⁴ was estimated in the following manner: 2 cc of a filtrate of the sample was placed in the cup of a Hellige colorimeter and made alkaline by the addition of 2 or 3 drops of 40 per cent sodium hydroxide. The color was then compared against an alkalinized standard solution of phenolsulphonphthalein of the original concentration taken with the test meal.

In 1923, one of us (Gorham⁴) described a procedure for estimating the dilution of the gastric juice by the fluid taken with the test meal and for determining the fluid motility of the stomach. The principal of this is as follows: little, if any, water is absorbed in the stomach. This is also apparently true of certain dyes, such as phenolsulphonphthalein. If this is a fact and a fixed quantity of water (400 cc) containing a definite amount of phenolsulphonphthalein (6 mg) is given as part of the test meal, the percentage of dye concentration in a sample of the contents of the stomach at a given period after ingestion of the test meal may be interpreted to approximate the dilution of the gastric juice by the fluid taken with the test meal. The total amount of dye solution remaining in the stomach at a given time after the meal is an index to the fluid motility of the particular stomach under given conditions.⁵

By "corrected acidity" and "corrected total chlorides" are meant the acid and chloride concentration in a sample of gastric contents after removal of the factor of test meal dilution.

Example—If the dye concentration in the sample of gastric contents is 50 per cent of the dye concentration of the fluid taken with the test meal, it is obvious that in 100 cc of gastric contents, 50 cc is water taken with the test meal, and only 50 cc can be related directly to gastric secretion.

$$\frac{60 \text{ degrees (acidity as ordinarily obtained)} \times 100}{100-50 \text{ (per cent dilution)}} = 120 \text{ degrees}$$

3 One-tenth gram of sodium chloride is capable of producing approximately 171 cc of tenth-normal hydrochloric acid or vice versa.

4 Gorham, F. D. The Factor of Dilution in Gastric Analysis, *J. A. M. A.* 82:1738 (Nov.) 1923.

5 This procedure is not to be confused with the method described in 1926 by Bloomfield and Keefer (*Arch. Int. Med.* 37:819 [June] 1926). They also used a dye, but attempted to make a quantitative estimation of gastric secretion.

TABLE 1—Data of Normal Subjects

	Phenol- sulphon phthalein, per Cent	Free Hydro- chloric Acid	Total Acid	Total Chlorides	Corrected for Test Meal Dilution			Bile
					Free Hydro- chloric Acid	Total Acid	Total Chlorides	
Case 1 (M M H)								
Contents during fasting		0	24	91				Negative
30 minutes	78	5	7	24	23	32	93	1 plus
60 minutes	40	9	11	55	15	18	91	1 plus
90 minutes	10	37	50	94	40	56	104	Trace
120 minutes	0	40	50	90	40	50	90	Negative
150 minutes	0	33	44	94	33	44	94	Negative
Case 2 (C M S)								
Contents during fasting		0	12	89				Negative
30 minutes	52	24	32	71	50	66	106	Trace
60 minutes	30	25	38	72	40	74	102.5	1 plus
90 minutes	10	30	40	85	33	44	94	Negative
120 minutes	0	29	38	102	29	38	102	Negative
Case 3 (A S)								
Contents during fasting		18	34	124.3				Negative
30 minutes	75	20	26	33	80	92	133	Trace
60 minutes	21	54	65	85.5	62	89	107	1 plus
90 minutes	0	60	73	107	60	73	107	2 plus

Diagram 1

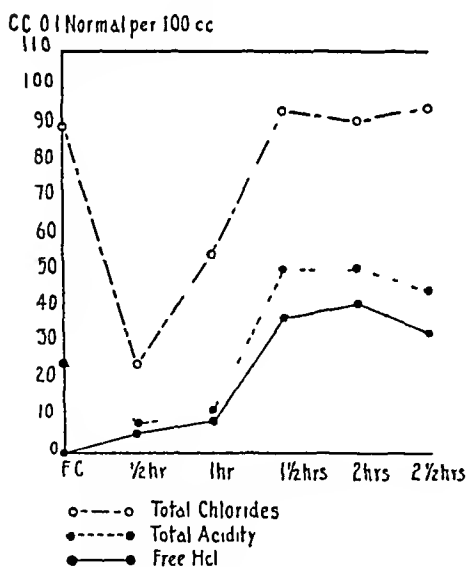


Diagram 2

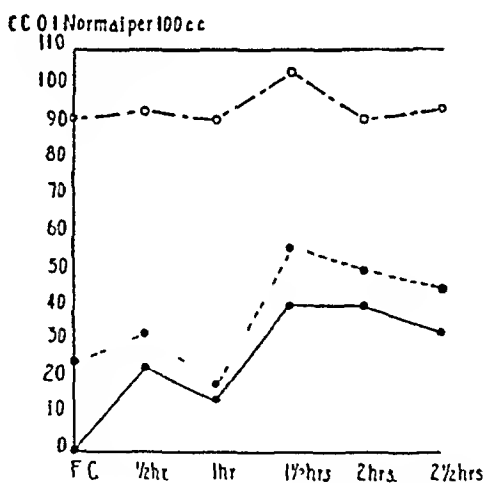


Chart 1—Graphic illustration of case 1, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degree of free hydrochloric acid, total acidity, and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, the total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc of distilled water and 6 mg of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. Compare the chloride level with the acidity.

and if 60 degrees is the total acidity of the diluted sample as ordinarily obtained, then the "corrected total acidity" would be 120 degrees, which more nearly represents the acidity of the undiluted gastric juice

RESULTS OF EXPERIMENTS

From a study of table 1 and charts 1, 2 and 3, a comparison may be made of the chloride concentration, the acidity and their relationship to one another in the contents of the stomach during fasting and in the gastric chyme at different digestive periods after the test meal. A comparison of diagrams 1 and 2 in charts 1, 2 and 3 illustrates diagrammatically the influence of the factors of test meal dilution and gastric motility on the character of the so-called "acid secretion curve," as obtained by the fractional method of gastric analysis. It is noted in

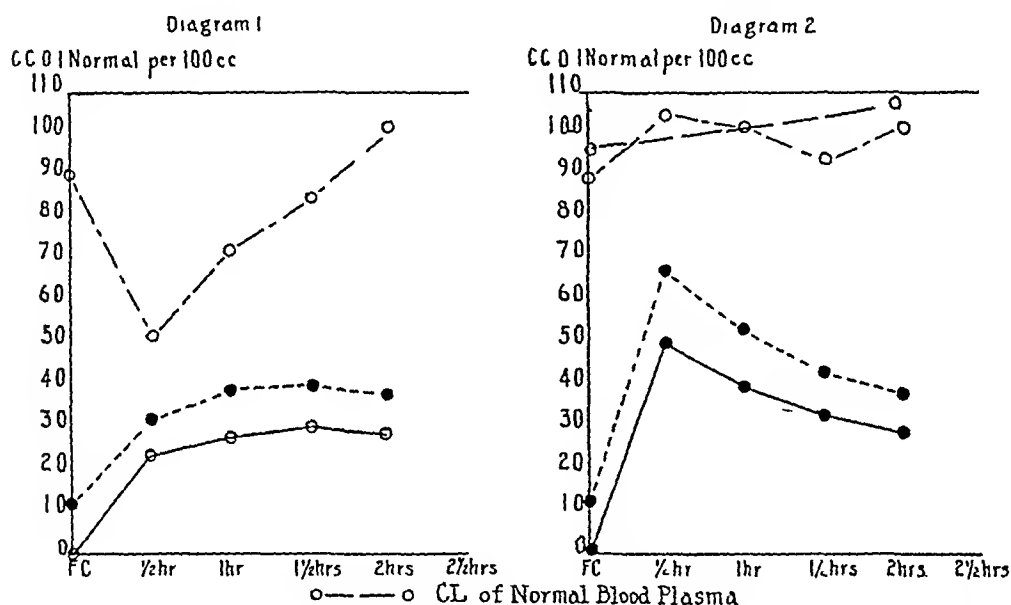


Chart 2—Graphic illustration of case 2, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc of distilled water and 6 mg of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the contents of the stomach during fasting and of the gastric chyme at different digestive periods after the test meal. In diagram 2, compare the chloride level of the gastric contents with the chloride concentration of normal blood plasma (approximately 100 degrees).

these subjects that the chloride concentration of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution approaches a similar level. A definite relationship does not exist between the acidity and total chloride concentration, the chlorides showing less fluctuation than the acidity.

In a subject in whom gastro-enterostomy had been successfully performed (table 2 and chart 4), a liquid test meal, as evidenced by the disappearance of the dye in the sample, left the stomach within thirty minutes after ingestion, denoting a relative fluid hypermotility. In this and similar subjects was found a marked variation between the free hydrochloric acid and the chloride levels.

TABLE 2—Data of Patient (C D) in Whom Gastro-Enterostomy for Ulcer Was Performed

	Phenol sulphon- phthalein, per Cent	Free Hydro- chloric Acid	Total Acid	Total Chlorides	Corrected for Test Meal Dilution			Bile
					Free Hydro- chloric Acid	Total Acid	Total Chlorides	
Contents during fasting,		18	32	106				
30 minutes	20	23	27	87	20	35	111	1 plus
60 minutes	0	22	31	111	22	31	111	1 plus
90 minutes	0	21	26	109	21	26	109	2 plus
120 minutes	0	31	31	106	31	31	106	2 plus

Diagram 1

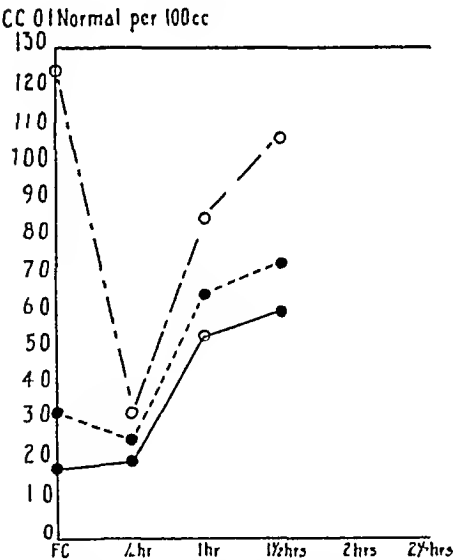


Diagram 2

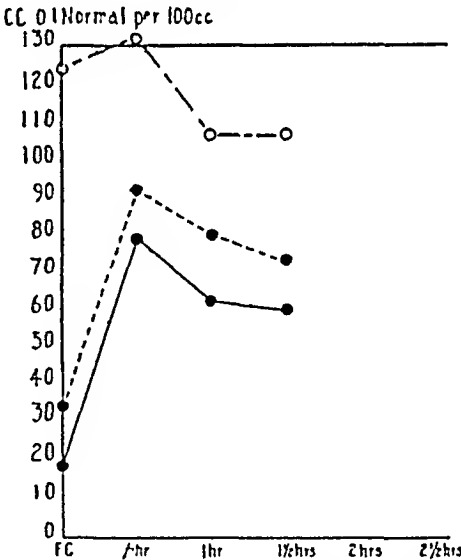


Chart 3—Graphic illustration of case 3, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc of distilled water and 6 mg of phenolsulphonphthalein are shown. Note the influence of the test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2 note the concentration level of the total chlorides of the contents of the stomach during fasting and of the gastric chyme at different digestive periods after the test meal. Compare the chloride level with the acidity.

TABLE 3—Data of Patient (Mrs N) with Achylia Gastrica

	Phenol-sulphon-phthalein, per Cent	Free Hydrochloric Acid	Total Acid	Total Chlorides	Corrected			Bile
					Free Hydrochloric Acid	Total Acid	Total Chlorides	
Contents during fasting		0	2	62	0	2	62	Negative
30 minutes	70	0	4	24	0	13	78	Negative
60 minutes	40	0	10	35	0	17	57	Negative
90 minutes	20	0	8	62	0	12	77	Negative
120 minutes	0	0	8	67	0	10	68	Negative

TABLE 4—Protocols of Normal Medical Students

Subject	Fasting			Test Meal			
	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
B	3	17	89.1	45	21.6	34.3	88.9
C O	4	13	76.35	30	25	33.5	69.1
F S	7	11.5	70.5	32	26	35.5	74.5
L H	10.5	21	99.8	30	13.5	20	91.3
P R	8	13.5	84.6	40	35.3	43.5	79.6
H K	Negative	11.3	99.1	35	13.4	25.1	100.5
W	3	8	106.35	30	19.5	26	102.2
L W	8.5	14.3	89.3	40	27.5	43.3	84.1
H A	3	14.7	105.6	25	16.7	24.1	100.8
L E	0	18.1	87.31	30	6	19.5	84.1
D	16.5	27	101.3	40	32	41	109.3
S	Negative	12.5	113.1	35	13	26.5	112.6
S H	6	14.5	113.4	30	32.1	43.4	111.5
S	Negative	6	95.5	40	13.5	23	99.5
S A	0	10	79.3	43	11	18.5	81.2
G M	6	13.5	81.4	20	12.1	19.3	86.2
H M	17	26.5	98.7	25	24.5	33.1	99.1
F W	21.4	29.5	101.6	35	36	43	110.1
H T	16.1	24.3	87.1	26	22	29.1	92.15
P R	0	12	89.1	23	17.1	24.6	84.5
J C	9.1	16.3	84.1	20	19.1	23.1	91.3
C C	8.1	17.4	99.3	22	16	24	97.6
G L	17.9	28.4	93.1	40	24	36	99.15
Average	7.2	16.5	92.95	27.6	16.4	30.1	89.91

TABLE 5—Protocols of Patients with Duodenal Ulcer

Subject	Fasting			Test Meal			
	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
R M	45	56	136.5	30	48	53	119.3
F A H	28	30	119.7	9	35	40	109.4
J C P	36	42	136.1	30	40	55	132.8
F A C	2	5	133.6	10	34	50	138.4
W H	28	36	95.5	10	50	61	102.7
A M L	40	42	129.4	18	52	60	135.8
W H R	30.4	40	102.3	25	18	29	106.8
R H B	36	42	112.6	30	38	44	119.7
C K C	18	30	102.6	18	20	38	119.7
L H P	15	21	106.7	10	20	30	111.7
J A H	25	32	119.6	9	38	40	123.1
H S	29	33	100.8	15	44.7	54.1	98.7
W W	70.5	85	130.4	15	85.8	96	129.9
D E	32	48	116.3	20	51.2	62.5	127.2
W C B	68	72	136.6	10	90	106	149.6
F C R	60	68	136.8	42	70	75	139.4
G W S	31	34	119.7	30	9.3	17	122.6
A D	6	14	112.7	15	61	80	114.9
M C	37	48	119.9	52	41.6	54	125.3
Average	33.5	40.9	119.3	20.9	44.5	51.9	122.4

TABLE 6—*Protocols of Patients with Disease of the Biliary Tract*

Subject	Fasting			Test Meal			
	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
M F	0	6	102.6	22	11	19	111.2
J O B	16	22	136.8	23	10	60	139.7
A F H	28	37	120.7	25	42	58	137.8
J D	0	5	93.2	19	0	12	95.5
L M G	0	6	101.2	8	8	16	95.5
W T T	15	50	116.4	20	2	6	119.1
S F	6	8	119.7	40	26	38	133.7
A A R	0	2	122.4	38	42	50	137.5
C A T	19	22	98.7	10	52	40	104.8
P B	68	71	136.6	17	53	70	128.2
C A J	19	22	87.2	20	40	50	110.5
J R	0	6	119.7	20	20	28.7	121.2
J A	0	16	119.5	15	18.2	28	128
E W		No fasting		10	35	46.6	90
J G	21	41	116	7	11.6	26.2	106
M R	7.5	7.6	81.1	22	15	19.6	78.2
I G	8	16	96.4	12	10.2	12.5	101.4
Average	12.8	19.8	101.2	19.5	23.9	34.2	114.1

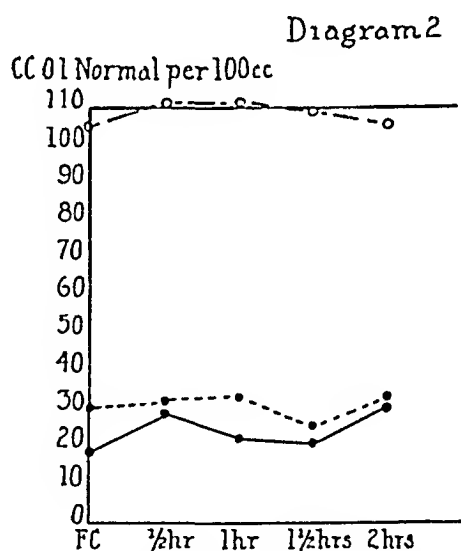
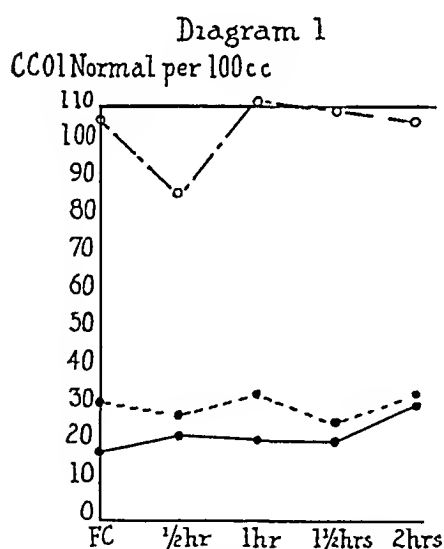


Chart 4—Graphic illustration of table 2. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc of distilled water and 6 mg of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. In diagram 2 (corrected), note particularly the relationship of the total chloride concentration level and acidity.

In certain pathologic states (table 3 chart 5 and table 7) such as are found in subjects with achylia gastrica (pernicious anemia) the average chloride concentration as compared with that of normal persons (tables 1 and 4) was lower. In duodenal ulcer disease of the biliary tract and benign pyloric obstruction (tables 5, 6 and 8) there was found a higher level as compared to normal but no higher than found in a group of miscellaneous cases.

TABLE 7—*Protocols of Patients with Achylia Gastrica*

Subject	Fasting			Test Meal			
	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
M	0	3	44	10	0	7	49.5
T R	0	8	47.4	15	0	9.5	53.2
W	0	5	47	20	0	8.3	49.1
E W	0	5	63.1	18	0	7.4	58.4
S	0	7.9	49.1	15	0	15	52.1
J W	0	8	63.1	20	0	11	63.4
H P	0	6.5	63.1	15	0	9.5	59.1
L O	0	8.7	58.2	20	0	11.2	54.2
T R	0	10.5	62.5	Trace	0	12	47.4
Mrs N	0	6.5	68.4	10	0	11.2	64.1
N I	0	6.8	61.2	9	0	10.3	57.2
Average	0	7.8	60.1	12.4	0	10.2	57.9

Diagram 1

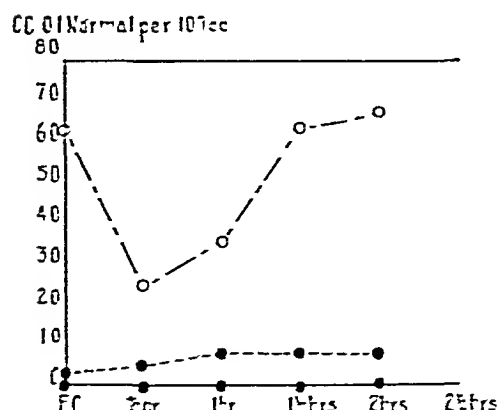


Diagram 2

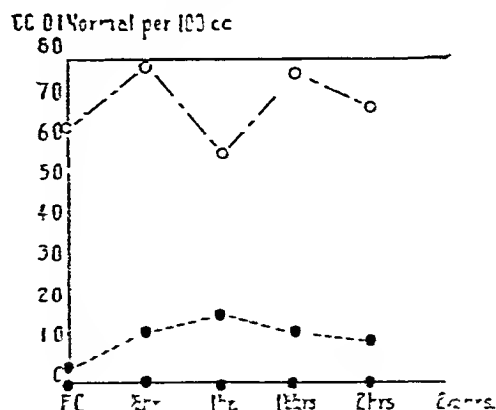


Chart 5—Graphic illustration of table 3. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc of distilled water and 6 mg of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. In diagram 2 (corrected for test meal dilution) note particularly the relationship of the total chloride concentration level, free (achlorhydria) and total acidity.

TABLE 8—*Protocols of Miscellaneous Group of Patients*
Test Meal

	Corrected Free Hydro chloric Acid	Cor rected Total Acidity	Cor rected Total Chlorides		Corrected Free Hydro chloric Acid	Cor rected Total Acidity	Cor rected Total Chlorides
Hyporeidity	14.5	21.8	71.8	Chronic appendicitis	58	67	163.2
Hyporeidity	10	15	147.9	Chronic appendicitis	68	77	191.2
Hyporeidity	20	36	187	Chronic appendicitis	22	34	87.5
Hyporeidity	8.5	30	144.5	Chronic appendicitis	88	102	157
Hyporeidity	9.3	17	132.6	Chronic appendicitis	38	54	151.2
Hyporeidity	11.6	26.6	106	Migraine	12	33	123.12
Hyperacidity	70	77	146.2	Colitis	45	63	147.9
Hyperacidity	70	90	121.5	Colitis	51	65.4	102
Hyperacidity	82	112.4	122.6	Simple goiter	26	62	149.6
Hyperacidity	88	102	151.7	Gastro enterostomy	28	52	144
Hyperacidity	90	106	149.6	Gastro enterostomy	40	69	139.9
Hyperacidity	68	90	146	Gastro-enterostomy	108	158	186.7
Simple anemia	41	88	110.4	Gastro enterostomy	42	53	146.8
Simple anemia	36	64	153.9	Gallstones	24	12	174
Simple anemia	10	15	144.9	Neurosis	38	44	136.8
Benign pyloric obstruction	75	103	231	Neurosis	20	36	187
Benign pyloric obstruction	71	85	170	Chronic myocarditis	5	46	122
Benign pyloric obstruction	45	59	144	Chronic pyelitis	66	78	153
Constipation	51	75	187	Postoperative adhesions	53	67	151.3

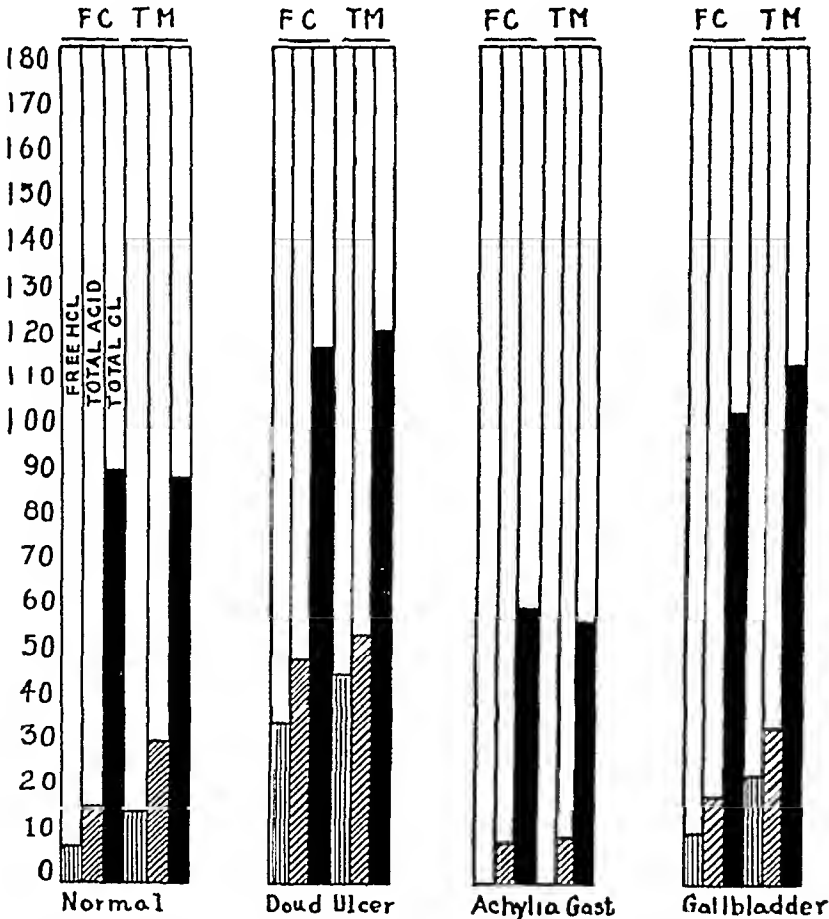


Chart 6—Graphic illustration of tables 4, 5, 6 and 7. Compare degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution. Aspiration of contents forty-five minutes after test meal.

Tables 4 5 6 7 and 8 and chart 6 illustrate the results obtained by the use of the single aspiration procedure. From these tables, it is possible to make a comparative study of data obtained from subjects representing both normal and pathologic conditions.

COMMENT

From our observations we agree with Bolton and Goodheart that the absence of free hydrochloric acid or the presence of a low active hydrochloric acid concentration in the contents of the stomach is not necessarily an indication that gastric secretion is correspondingly diminished and that in persons with achlorhydria the total chlorides of the contents of the stomach may be of normal concentration. We can hardly agree, however, with the assumption that when the total chlorides are at a normal level it may be assumed that a low acidity is necessarily due to excessive neutralization.

Baird and Campbell stated that diminished gastric secretion can be distinguished from normal secretion with excessive neutralization by a comparative study of the total chloride concentration and acidity of the stomach contents. We do not concur in this opinion, as it cannot be assumed that the chlorides of the contents of the stomach are necessarily a volumetric index to the production of hydrochloric acid by the gastric glands. From a study of the subjects with achylia gastrica (table 7) it is obvious that in some instances a chloride concentration approaching the normal level was encountered. During investigation it was found that the chloride concentration of the duodenal contents obtained by means of the duodenal tube and bile taken from the common duct and the gallbladder at operation was as high or higher than that of the contents of the stomach; therefore, the regurgitation of the intestinal fluids into the stomach is in some instances an important factor in determining the height of the chloride level in the gastric contents.

It was noted that the total chloride concentration of the fasting contents and of the gastric chyme at different digestive periods after correction for dilution frequently approached similar levels. In the normal subjects a similarity was noted between the chloride level of the contents of the stomach and that found in normal blood plasma. It is noted from a comparative study in subjects showing hypoacidity and hyperacidity (table 8) that the chloride level may be similar in the two conditions.

In relation to this investigation we would call attention to the work of Gamble and McIver⁶ who estimated the total chlorides and total bases of gastric juice obtained from pouches made in the fundic and

⁶ Gamble J L and McIver M A. Fixed Base in Gastric Juice. J Exper Biol & Med 23:439 (March) 1926

pyloric region of the stomach in animals. They observed that during different phases of digestion the chlorides were nearly stationary, while there was a wide range in the variation of the total bases.⁷

SUMMARY

1 In the subjects without symptoms of disease, the total chloride concentration of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution frequently approached the same level, in many instances this concentration showed a similarity to that of normal blood plasma.

2 The chloride concentration of the contents of the stomach during fasting and of the gastric chyme was variable in different pathologic conditions, a fairly constant increase being found in pyloric obstruction, duodenal ulcer and disease of the biliary tract. In achylia gastrica, the total chloride concentration was usually low but in some instances approached the average level found in normal persons.

3 The relationship of the acidity and total chlorides of the contents of the stomach during fasting and of the gastric chyme after the standard test meal was exceedingly variable in both health and disease. The acidity showed a greater fluctuation than the chloride concentration, this being especially noteworthy in subjects showing hypoacidity, hyperacidity and those in whom gastro-enterostomy had been successfully performed.

4 From our experimental study, especially in subjects showing achylia gastrica, it would appear that the chloride concentration of the contents of the stomach as determined by the direct Volhard method is not necessarily a volumetric index to the production of hydrochloric acid by the gastric glands.

⁷ We take this opportunity to acknowledge the assistance given us in this investigation by Dr. Ethel Ronzoni, of the Department of Internal Medicine.

GASTRIC SECRETION

ITS ALTERATION BY THE USE OF ATROPINE, EPINEPHRINE AND PILOCARPINE

A M ALTSHULER, M D

DETROIT

Pharmacologic substances which act on the sympathetic and parasympathetic nervous system, particularly those which act on the nerve supply of the gastro-intestinal tract, have been investigated extensively. The explanation for this lies in the various therapeutic applications to which such knowledge could be directed, as well as in the fact that numerous conflicting reports of results of similar experiments have led to the desire to arrive at the truth by further study. A brief résumé of the more important investigations which have been carried out with atropine, epinephrine and pilocarpine will aid materially in interpreting the results of this study. A review of the work of other investigators reveals plainly the conflicting conclusions drawn from these experiments.

ATROPINE

In 1882, Netchaev,¹ working in Pavlov's laboratory, found that atropine paralyzes gastric secretion. This work was later confirmed by Ushakov² who showed that atropine paralyzed the gastric secretion in animals during the first (cephalic) stage of secretion whether initiated by sham feeding or by stimulation of the vagus nerve by means of an induction current. Sanotzki³ showed that in the second stage (gastric phase) of gastric secretion, atropine diminished the secretion, provided the stimulant to secretion was in the stomach itself or in the isolated pylorus. If, however, the chemical stimulants to secretion were introduced hypodermically or intravenously, then atropine did not affect it.⁴ Riegel⁵ found a diminished gastric secretion with the

1 Netchaev, A. A. On the Inhibitory Action of Atropine, Morphine and Chloral Hydrate upon the Gastric Secretion and the Stimulation of the Sensitive Nerves, Diss., St. Petersburg, 1882.

2 Ushakov, V. G. On the Action of the Nerve Vagus upon the Gastric Secretions in a Dog, Diss., St. Petersburg, 1896, p. 20.

3 Sanotzki, A. S. The Stimulation of the Gastric Secretions, Diss., St. Petersburg, 1892, p. 80.

4 Zehony, G. P., and Savitch, V. V. On the Mechanism of the Gastric Secretion, Tr. Obshche Russk. Vrach. 79 1, 1911-1912, Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. 150 128, 1913.

5 Riegel, A. Ueber Medicamentöse Beeinflussung der Magensecretion, Ztschr. f. klin. med. 37 381, 1899.

use of atropine, while Bylina ⁶ found that it diminished gastric secretion only in cases of hypersecretion. Auer and Meltzer ⁷ stated that atropine causes paralysis of the vagus endings connected with Auerbach's plexus, with a resultant diminution of secretion. Gerhard Katsch ⁸ has shown that small doses of atropine stimulate Auerbach's plexus and at the same time paralyze the nerve endings of the vagus with a resultant decrease in peristalsis. Lasch ⁹ found that injections of atropine had two separate and opposite actions, first, an increase in peristalsis which lasted only a few minutes, and second, following this increase, a prolonged stage of inhibition of peristalsis which ended in complete atony. He explained this apparent paradox by stating that atropine first produces a transitory stimulation of the parasympathetic system, and later paralysis of the parasympathetics. Zung and Tysebaert,¹⁰ working with dogs, observed diminished contractions of the stomach after injections of atropine. Small doses did not have any effect on the contractions, but they did result in lessened tonus. Klee ¹¹ observed in animals, and Otvos ¹² observed in man, increase in pylorospasm and a delayed emptying of the stomach following injections of atropine. Stranz ¹³ confirmed Otvos' observations on the prolongation of the evacuation time. Hecht,¹⁴ experimenting with the isolated stomach of rats, found that the action of atropine was variable. He explained this variability by the presence or absence of peristalsis inducing substances, and of choline in particular. Kalk and Siebert ¹⁵ did not find any changes in the hydrochloric acid concentra-

6 Bylina, A. On the Analysis of the Disturbance of Gastric Secretion, *Russk. Vrach* **12** 83, 1913.

7 Auer, J., and Meltzer, S. J. Action of Ergot upon the Stomach and Intestines, *Am. J. Physiol.* **17** 143, 1906.

8 Katsch, Gerhard. Beiträge zum Studium der Darmbewegungen. 3. Pharmakologische Einflüsse auf den Darm (bei physiologischen Versuchsanordnung), *Ztschr. f. exper. Path. u. Therap.* **12** 253, 1912-1913.

9 Lasch, C. H. Röntgenologische Untersuchungen über den Einfluss des Atropins auf die Magenmotilität, *Klin. Wchnschr.* **17** 840, 1922.

10 Zung, E., and Tysebaert, J. Action of Atropine Sulphate on Isolated Stomach and Intestines, *J. Pharm. and Exper. Therap.* **8** 325, 1916.

11 Klee, P. Beiträge zur pathologischen Physiologie der Mageninnervation. 2. Pylorus Insuffizienz und praepylorischer Gastropasmus, *Deutsches Arch. f. klin. Med.* **133** 265, 1920.

12 Otvos, E. Beiträge zur pharmakologischen Beeinflussbarkeit der Magenmotilität, *Klin. Wchnschr.* **4** 445, 1925.

13 Stranz, J. Untersuchungen über die diagnostische Brauchbarkeit der Atropinprobe des Magens, *Med. Klin.* **2** 59, 1926.

14 Hecht, P. Untersuchungen über die Wirkung des Atropin auf den überlebenden Magen, *Deutsches Arch. f. klin. Med.* **136** 296, 1921.

15 Kalk, H., and Siebert, P. Untersuchung über die Wirkung von Atropin und Belladonna (Bellafohn) auf die Magenfunktion, *Arch. f. Verdauungskr.* **40** 313, 1927.

tion after atropine had been given. They also confirmed the observations of Katsch and Kalk¹⁶ that the acidity of the gastric juice is not influenced by atropine and that the evacuation time of the stomach is prolonged following an injection of atropine. They did not find any regular decrease in acidity with atropine; the majority of their determinations in fact, showed an increase. Keeton, Luckhardt and Koch,¹⁷ on the contrary, experimenting on dogs with a Pavlov stomach, found that atropine inhibits the gastric secretion. They emphasized that from 50 to 80 per cent of the total gastric secretion was arrested before the hydrochloric acid dropped. Rehfuss¹⁸ also found that large doses of atropine given hypodermically caused a decrease in psychic secretion and in the gastric acidity but it never resulted in complete disappearance of the secretion. Pokras and Michelson,¹⁹ applying the method of investigation of Bylina (in which the reflectoric stage of digestion was eliminated) found that atropine was a potent substance in diminishing hypersecretion. Crohn²⁰ on the other hand, stated that 1/65 gram (0.00101 Gm) of the drug given hypodermically one-half hour after eating did not affect the motility of the stomach, but raised the average of acidity from 32 acid per cent to 75, while Lockwood and Chamberlin²¹ stated that atropine depresses both the secretory and motor activity of the stomach. Pongs²² noted a diminished gastric secretion and a prolonged emptying time of the stomach after the administration of atropine and his observations are confirmed by Rall.²³ Keefer and Bloomfield²⁴ found that the amount of gastric secretion was less after atropine had been administered than when it was not

16 Katsch, G. and Kalk, H. Zum Ausbau der Kinetischen Methode für die Untersuchung des Magenchemismus. 3. Mitteilung die Chloride des Magensaftes besonders bei Salzsäuremangel, *Klin. Wchnschr.* 5:881, 1926.

17 Keeton, R. W., Luckhardt, A. B., and Koch, F. C. Gastrin Studies. 4. The Response of the Stomach to Food and Gastrin Bodies as Influenced by Atropine. *Am. J. Physiol.* 51:469, 1920.

18 Rehfuss, M. E. Action of Atropine on Gastric Secretion, *Tr. Sect. Gastro-Enterol. & Proct., A. M. A.* 25, 1918.

19 Pokras, S. and Michelson, V. Vegetatives Nervensystem und Magen-secretion, *Arch. f. Verdauungen* 38:373, 1926.

20 Crohn, B. B. Studies in Fractional Estimation of Gastric Contents, *Am. J. M. Sc.* 155:801, 1918.

21 Lockwood, B. C. and Chamberlin, H. G. The Effect of Atropin on Gastric Function. *Arch. Int. Med.* 30:806, 1922.

22 Pongs. Die Beeinflussung der Säureverhältnisse des Magens durch Atropin. 33. Kongress d. Deutsch. Ges. f. inner. med. 1921, p. 452.

23 Rall, T. Ueber den Einfluss des Atropins auf die secretorische und motorische Function des gesunden Magens, *Ztschr. f. d. ges. exper. Med.* 52:752, 1926.

24 Keefer, C. S. and Bloomfield, A. L. Effect of Atropine on Gastric Function in Man. *Arch. Int. Med.* 38:303, 1926.

given. They emphasized that the type of secretion was markedly altered by atropine. They pointed out that normally there is a great variation in the emptying time of the stomach as determined by their method, and these variations are also present after the administration of atropine.

EPINEPHRINE

The experiments with epinephrine in man as well as in animals also yields contradictory results. The action of epinephrine on the motor activity of the stomach results in a picture identical with the so-called "sympathetic stomach." Elliot²⁵ has shown in animals, that injections of epinephrine makes the stomach large, flaccid and weak in peristalsis. Katsch²⁶ observed the same thing in man, the entire stomach relaxing and the emptying of the stomach retarded following its use. Klee,²⁷ confirmed these observations in roentgen-ray study of cats. Bickel,²⁸ however, stated that there is a preliminary stage after the injection of epinephrine in which the tonus of the stomach is increased, the relaxation coming later in the second stage. Kolm and Pick²⁹ observed an "inverse" vagotropic action following the use of epinephrine. Yukawa,³⁰ G. Sirotinin,³¹ and Loeper and Verpy³² all found an increase in gastric secretion following injection of epinephrine. The latter two investigators found the hydrochloric acid increased. Opposed to this, is the observation of Hess and Gundlach³³ who found always an inhibition of secretion following the injection of epinephrine, and of Thomas³⁴ who found that epinephrine increases the tonus of the pyloric sphincter when the latter is relaxed and decreases the tonus when it is contracted. Badylkes³⁵ found that epinephrine increases the gastric

25 Elliot, T. R. The Action of Adrenalin, *J. Physiol.* **32** 401, 1905

26 Katsch, G. Der Menschliche Darm bei pharmakologischer Beeinflussung seiner Innervation, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **21** 157, 1914

27 Klee, P. Beiträge zur pathologischen Physiologie der Mageninnervation, *D. Arch. f. klin. Med.* **128** 204, 1919

28 Bickel, A. Der Nervöse Mechanismus der Secretion der Magendrüsen und der Muskelbewegungen am Magendarmkanal, *Ergbn. d. Physiol.* **24** 228, 1925

29 Kolm, R., and Pick, E. P. Ueber der Änderung der Adrenalinwirkung nach Erregung der Vagalen Endapparate, *Arch. f. d. ges. Physiol.* **184** 79, 1920

30 Yukawa, G. Klinisch-experimentelle Untersuchungen der Adrenalinwirkung auf die Magendrüsen, *Arch. f. Verdauungskr.* **14** 166, 1908

31 Sirotinin, B. Action of Adrenalin on the Secretion of a Heidenham's Stomach of a Dog, *Wratchebnoje Dielo* **18** 24, 1923

32 Loeper, M., and Verpy, G. L'action de l'adrenalin sur le tractus digestif, *Compt. rend. Soc. de biol.* **53** 793, 1917

33 Hess, W. R., and Gundlach, R. Der Einfluss Adrenalins auf die Secretion des Magensaftes, *Arch. f. d. ges. Physiol.* **185** 122, 1920

34 Thomas, J. E. The Action of Adrenalin on Pyloric Sphincter, *Proc. Soc. Exptl. Biol. & Med.* **23** 748, 1925-1926

35 Badylkes, S. O. Klinisch-physiologische Beobachtungen über den Einfluss einiger Hormone auf die Magensecretion (Experimentelle Untersuchung), *Arch. f. Verdauungskr.* **34** 105, 1924

acidity in 80 per cent of his cases and decreased it in 20 per cent. Michelson and Neumaik³⁶ stated that epinephrine increases gastric acidity in normal conditions, while in cases of hypersecretion the acidity is lowered. Dixon³⁷ noted contraction of the frog's stomach following an intravenous administration of epinephrine, while Cushny³⁸ noted inhibition of all gastric motility immediately after its injection. Petrovic³⁹ showed experimentally that epinephrine does not hinder the evacuation of water from the stomach. Gruber⁴⁰ thought that the varying actions of epinephrine on the stomach depends on its concentration—weak solutions producing increase in tonus, stronger solutions producing inhibition.

PILOCARPINE

Tshurilov⁴¹ found that pilocarpine acted as a weak stimulant to the gastric glands. Doses of from 0.003 to 0.005 Gm hypodermically, which were sufficient to produce profuse secretion of saliva and mucus from the nose and stomach, did not have any effect on the gastric glands. Large doses, however, cause relatively greater secretion of the salivary glands than of the stomach (Zitovitch)⁴². Riegel⁴³ and Ehrmann⁴³ found an increase in the secretion of gastric juice following the administration of pilocarpine, but the acidity remained unchanged. Kljutcharev⁴⁴ reported its use in twelve cases in which he found a decrease in acidity following its administration in eight cases, unchanged acidity in one case, while in three cases, the acidity was raised. Kalk,⁴⁵ reported thirty cases, and stated that the acidity was diminished in the majority of them. Katsch and Egan⁴⁶ also found a decrease in

36 Michelson, V, and Neumark, I. E. Atropin, Adrenalin, Pilocarpin, und ihre Wirkung auf die Magensecretion und ihre Phasen, *Arch f Verdauungskr* **39** 275, 1926

37 Dixon, E. Effect of Adrenalin on Frog's Stomach, *J Physiol* **30** 97, 1903

38 Cushny, A. R. Pharmacology and Therapeutics, Philadelphia, 1918, p. 369

39 Petrovic, A. Ueber die Wirkung von Atropin und Adrenalin auf die Magenentleerung beim Menschen, *Deutsche med Wchnschr* **51** 1619, 1925

40 Gruber, C. M. The Effect of Epinephrine on Excised Strips of Frogs Digestive Tracts, *J Pharmacol & Exper Therap* **20** 321, 1922

41 Tshurilov, I. A. The Secretory Poisons in Regard to the Gastric Secretion, Diss., St. Petersburg, 1894

42 Zitovitch, I. S. The Action of Pilocarpin on the Secretion of the Gastric Glands, *Tr Obstschestva Russk Vrach* **69** 324, 1902

43 Ehrmann, R. Physiologische und Klinische Untersuchungen über die Magensaftsecretion. *Internationale Beitr z Path u Therap der Ernährungsstörungen* **3** 382, 1911-1912

44 Kljutcharev, S. On the Importance of Determining the Different Stages of Digestion in Accordance with the Clinical Observations, *Terapevtichesk Arch* **2** 3, 1924

45 Kalk, G. Ueber den Einfluss des Pilocarpins auf die Tätigkeit des Menschlichen Magens, *Arch d Verdauungskr* **32** 219, 1924

46 Katsch, G. Ueber Hyperacidität, *Klin Wchnschr* **18** 902, 1922

acidity following the administration of pilocarpine Bennett⁴⁷ reported conflicting results Michelson and Neumark³⁶ explained the decrease in gastric acidity by the increase in secretion of mucus and the delayed emptying time of the stomach with resultant dilution

The foregoing brief survey of the experimental work with atropine, epinephrine and pilocarpine reveals many discrepancies and much experimental data which seems conflicting or directly contradictory If the observations are accurate, these discrepancies can be accounted for only by assuming that the various experiments were carried out on stomachs that were in different functional states when the experiments were begun Zimnitzky⁴⁸ has shown that the action of drugs on functioning cells depends on what phase of activity those cells are in when the drug reaches them Thus, a drug which would result in stimulation of the cell's activity if acting on a cell at rest, could result a little later in perhaps increased stimulation, or, if the cell were already maximally stimulated, might even result in inhibition by exhausting the cell through the overload In other words, dependent on what phase of activity the cell were in, the same drug, acting on the same cell, might at one time result in stimulation, and at another time in inhibition By bearing this in mind, it is possible to reconcile apparently contradictory observations in regard to these vagotropic and sympathicotropic substances It is reasonable to assume that disturbances of the gastric secretion may be dependent on two essentially different bases, i.e., it may be that the secreting cells are normal cells, but due to local or constitutional factors they are kept in such a phase of activity that when a normal stimulus, such as food, reaches them, they do not react as would a normal cell at rest, but react abnormally, either by hypersecretion or by inhibition with a decrease or absence of secretion, or, again, the cells may be pathologic cells, which even at rest do not respond to ordinary stimuli as would normal cells

Other investigators⁵⁰ and I,⁴⁹ employing the method of Zimnitzky,⁴⁸ have demonstrated that, in general, there are characteristic types of secretion in various gastric and constitutional disturbances There is also a characteristic normal type of secretion As the same method was used in obtaining the results reported in this article a brief

47 Bennett, Isod The Modification of Gastric Function by Means of Drugs, Brit M J 1 366, 1923

48 Zimnitzky, S S Disturbance of the Secretory Function of the Glands of the Stomach, Moscow, 1926

49 Altshuler, A M A New Method of Gastric Analysis, Ann Clin Med 5 464, 1926

50 Gurvitch, I L On the Knowledge of the Function of the Gastric Cells Under the Influence of the Vagotrope and Sympatricotrope Substances, Trudy 7go s'ezda Therapevtov 7 280, 1925

description of the technic and of the types of gastric secretion differentiated by this method follows. A more detailed report can be found in one of my previous articles⁴⁹. The procedure is as follows. The patient is instructed to refrain from food or drink, starting at 6 00 p m of the day previously, at 8 00 a m a Rehfuß tube is introduced into the stomach. The contents of the fasting stomach are aspirated with the patient in various positions and the position of the tube is altered until all the contents are aspirated. The test breakfast of 200 cc of plain warm beef broth (400 Gm of lean beef in 1,000 cc of water) is given the patient who is instructed to sip it for a period of five minutes. Fifteen minutes after the breakfast is started, 10 cc of the contents of the stomach are aspirated. This is repeated every fifteen minutes for four times. Before each aspiration, the patient is requested to shake himself well. At the end of sixty minutes, the stomach is emptied, 200 cc of the same meat broth is given, and the same procedure is repeated for another sixty minutes. The contents are examined at once. The types of gastric secretion determined by this method are classified as follows: (1) The normal type. The characteristic of the normal type is that the sum of acidity for the second hour is greater than that of the first hour (average usually being from 15 to 25 per cent). (2) Asthenic type. Here the total figures for the first hour are greater than for the second. This may be even with cases of hyperacidity. (3) Inert type. This type is characterized by the fact that at the beginning, the response of the stomach cells to the stimulus is sluggish, but after the stimulus of the first test breakfast, administration of the second test breakfast causes a sudden increase in gastric secretion. Therefore, the work of the second hour is quantitatively decidedly greater than the first (up to 50 per cent). (4) The isosecretory type. Here the total amount of work for the first and second hour is the same. (5) Torpid type. In this case, neither the first nor the second test breakfast produces enough stimulation of the gastric cells to reveal the presence of free hydrochloric acid. In these cases, one must distinguish between functional and organic toipoi. In general, it can be shown that one of these types of gastric secretion tends to be characteristic in various local or constitutional disturbances.

In the present investigation, the type of secretion present was determined in each patient studied. After this had been done, allowing an interval of several days, the patient was given a subcutaneous injection of either atropine, epinephrine or pilocarpine together with the first test breakfast. Atropine was given in the form of 1/50 grain (0.00130 Gm) of atropine sulphate, epinephrine was given in the form of solution of epinephrine hydrochloride, 1-1000 in a dose of 1 cc, pilocarpine was given in the form of 1/4 grain (0.01620 Gm) of pilocarpine

hydrochloride A check on the action of the atropine was made by determining the dryness of the mouth, pharynx and larynx, by noting the changes in the pulse rate, dilatation of the pupil and dizziness. The action of the epinephrine was checked by noting the pulse rate, the blood pressure, paleness of the face, tremor, and by the result of the urinalysis. The physiologic activity of the pilocarpine was checked by noting the pulse rate, salivation, tearing, and nasal discharge, nausea and vomiting, diarrhea and flush of the face, and in all cases the subjective observations of the patient were determined.

The purpose of this study was to determine the effect, if any, of administering atropine, epinephrine and pilocarpine in altering the

TABLE 1—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	8	12	14	19
After 30 minutes	12	22	20	31
After 45 minutes	28	38	38	43
After 60 minutes	23	30	19	28
Total	71	102	96	124

TABLE 2—*Acidity of Contents of Stomach After Ingestion of Atropine Sulphate*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	19	6	12
After 30 minutes	25	28	18	25
After 45 minutes	28	40	18	32
After 60 minutes	21	28	12	19
Total	89	115	54	88

normal type of secretion in normal persons, and of their effect in altering the various abnormal types of secretion thought to be characteristic of certain gastro-intestinal and constitutional disturbances. Characteristic protocols in each group follow.

REPORT OF CASES

CASE 1—A H, a man, aged 44, had never had any gastro-intestinal complaints. The results of a general physical examination showed him to be normal. Urine analysis and stool examination were normal. Twelve cubic centimeters of the contents of the stomach was aspirated while the patient was fasting, the free hydrochloric acid was found to be 6 to acid phenolphthalein and the acidity was found to be 18 to acid phenolphthalein.

This same patient was given 1/50 grain (0.00130 Gm.) of atropine sulphate hypodermically at the time of the first test breakfast, when

the following determination was made a few days later. The results are shown in table 2

A few days later, the same patient was given $\frac{1}{4}$ grain (0.01620 Gm) pilocarpine hydrochloride hypodermically at the time of his first test breakfast. The results of the gastric analysis are shown in table 3

After an interval of a few days, the patient was given 1 cc of solution of epinephrine hydrochloride (1:1000) subcutaneously together with his first test breakfast. The results of gastric analysis are shown in table 4

TABLE 3—*Acidity of Contents of Stomach After Ingestion of Pilocarpine Hydrochloride Hypodermically*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	18	25
After 30 minutes	0	8	35	38
After 45 minutes	14	26	42	56
After 60 minutes	26	28	36	43
Total	40	68	131	162

TABLE 4—*Acidity of Contents of Stomach After Ingestion of Epinephrine Chloride Subcutaneously*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	28	36	6	14
After 30 minutes	32	39	32	43
After 45 minutes	42	54	23	34
After 60 minutes	34	44	15	21
Total	136	173	76	112

If the normal type of gastric secretion is compared with the gastric secretion in this type following the administration of atropine it is noted that following the stimulation by atropine, the secreting cells respond rapidly during the first hour, but soon become exhausted during the second hour, that is to say, under the influence of atropine, the normal type of secretion is converted into the asthenic type

After pilocarpine is given there is a sluggish secretion during the first hour, while during the second hour there is a gradual increase. Thus, pilocarpine converts the normal type of gastric secretion into the inert type. This observation may possibly account for the contradictory reports on the effect of pilocarpine on gastric secretion made by various investigators. Those who watched the first phase of the action of pilocarpine would report either inhibition of secretion or no alteration

of secretion, while those who observed the second phase of the gastric secretion for a longer period of time, would find an increase in secretion

After the administration of epinephrine, the gastric cells respond with an increased secretion during the first hour, while in the second hour, the secretion is sluggish. In other words, epinephrine converts the normal type of gastric secretion into the asthenic type.

The foregoing observations are in accord with those of Zimnitzky,⁴⁸ Gurvitch,⁵⁰ and Pshenitchnikov,⁵¹ who found that atropine and epinephrine converted the normal type of secretion into the asthenic type, while pilocarpine changed it into the inert type.

Similar studies were carried out with patients who demonstrated abnormal types of gastric secretion.

CASE 2—I R., a married woman, complained of gas, pressure in epigastrium, eructation, headaches localized in temples "like strokes of a hammer," and globus hystericus. This patient had a good appetite. The results of the

TABLE 5—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	7
After 30 minutes	0	6	0	9
After 45 minutes	0	12	0	10
After 60 minutes	0	8	0	10
Total	0	34	0	36

examination of the stool and urine were normal. No abnormality was noted on physical examination. Diagnosis of hysteria was made. The results of gastric analysis are shown in table 5. Twenty-four cubic centimeters of the contents of the stomach was aspirated while the patient was fasting, Guaiac was found to be negative, the free hydrochloric acid 4, and the total acidity 12.

It would be desirable, in this case, to have a method to determine with some degree of assurance whether this torpor belonged to the functional or to the organic group. With this in mind, the foregoing procedure was repeated a few days later, but at this time, 1 cc of epinephrine was given subcutaneously at the time of the first test breakfast. The results are shown in table 6.

By the use of epinephrine, the torpor was found to be a functional one, since the epinephrine converted the type of gastric secretion from one of torpor to the asthenic type. The gastric cells were still capable of responding with secretion, although they had been kept in such a

51 Pshenitchnikov, cited by Zimnitzky, S. Ueber die neue Methode der funktionellen Magenuntersuchungen und ihre Resultate, *Ztschr f d ges Exper Med* 44 181, 1924.

phase of activity that a normal stimulus was not any longer capable of stimulating them

In contrast with the foregoing case, is the following one in which the condition is diagnosed as carcinoma of the stomach

CASE 3—J H, a man, aged 51, an iron molder, had been complaining of pain in the epigastrium, lack of appetite and loss of weight during the past

TABLE 6—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	28	9	19
After 30 minutes	21	39	18	23
After 45 minutes	28	42	23	38
After 60 minutes	19	23	12	30
Total	80	132	62	110

TABLE 7—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	10
After 30 minutes	0	11	0	18
After 45 minutes	0	15	0	16
After 60 minutes	0	6	0	8
Total	0	40	0	52

TABLE 8—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	12	0	9
After 30 minutes	0	10	0	12
After 45 minutes	0	7	0	8
After 60 minutes	0	6	0	5
Total	0	35	0	34

eight months. He first consulted a chiropractor whose manipulation of the vertebrae did not improve his condition. When first examined by a physician, a mass about as large as a golf ball was found in the epigastrium, above and to the right of the umbilicus. Roentgen-ray diagnosis was carcinoma of the pylorus. Gastric analysis and other laboratory observations confirmed this diagnosis. Three hundred and twenty cubic centimeters of foul smelling contents of the stomach was aspirated while the patient was fasting; there was not any free hydrochloric acid found, the total acidity was 15. The results of the gastric analysis are shown in table 7.

The result of the gastric analysis after the administration of epinephrine with the first test breakfast are shown in table 8.

Thus the torpor of organic origin is unaffected by the administration of epinephrine. The results of gastric analysis of the same patient after injection of atropine at the time of the first test breakfast is shown in table 9.

The results of gastric analysis in this patient after the administration of pilocarpine are indicated in table 10.

TABLE 9—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	0	6
After 30 minutes	0	10	0	9
After 45 minutes	0	12	0	9
After 60 minutes	0	8	0	7
Total	0	36	0	31

TABLE 10—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	1	0	4
After 30 minutes	0	6	0	6
After 45 minutes	0	8	0	6
After 60 minutes	0	8	0	6
Total	0	36	0	31

TABLE 11—*Acidity of Contents of the Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	10	12
After 30 minutes	8	21	15	20
After 45 minutes	12	24	32	45
After 60 minutes	16	20	27	36
Total	36	73	84	113

Evidence is presented then, that where the torpor is organic, neither atropine, pilocarpine nor epinephrine can stimulate the gastric cells to secretion.

CASE 4—K. D., aged 47, complained of epigastric discomfort, feeling of fulness, eructation of gas with fetid odor, bad taste in the mouth, occasional nausea and vomiting. He was generally constipated, but occasionally had attacks of diarrhea. A diagnosis of pulmonary tuberculosis was made. The results of gastric analysis are shown in table 11. Twenty-two cubic centimeters of the contents of the stomach was aspirated while the patient was fasting, the free hydrochloric acid was found to be 8 and the total acidity was found to be 24.

The gastric reaction in the foregoing case falls into the inert hyposecretory type. A few days later, atropine was injected into the patient at the time of the first test breakfast, with the results shown in table 12.

After atropine has been given, an inert hyposecretory type of secretion remains unchanged as to type, but the work of the gastric cells

TABLE 12—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	9
After 30 minutes	0	10	4	14
After 45 minutes	4	16	12	28
After 60 minutes	6	22	32	52
Total	10	56	48	103

TABLE 13—*Acidity of Contents of Stomach After Ingestion of Epinephrine Hydrochloric Acid*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	6	14
After 30 minutes	0	6	11	20
After 45 minutes	8	18	18	26
After 60 minutes	12	23	16	21
Total	20	53	53	81

TABLE 14—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	12	0	4
After 30 minutes	0	8	0	6
After 45 minutes	0	8	0	10
After 60 minutes	0	4	0	6
Total	0	32	0	26

is considerably diminished by its use. One must assume that in this case, secreting cells that are already fatigued, react with even less work when further stimulated. As stated previously the phase of activity in which the drug finds the cell when it reaches it, determines whether the drug produces increased or diminished secretion.

The foregoing test was repeated using epinephrine instead of atropine, with the results shown in table 13.

The effect of epinephrine in this case, is essentially the same as that of atropine. Pilocarpine was next administered after an interval of a few days, with the results shown in table 14.

The overstimulation of gastric cells that were already fatigued, resulted in complete inhibition due to overloading the cell. In short, functional torpor has been produced in this case of an inert hyposecretion by the use of pilocarpine.

CASE 5—T L, aged 32, a married woman, complained of weakness, visual disturbance and loss of appetite. Her skin had a lemon-yellow tint. The result

TABLE 15—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	16	0	31
After 30 minutes	0	22	0	32
After 45 minutes	0	21	0	32
After 60 minutes	0	20	0	empty
Total	0	79	0	95

TABLE 16—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	17	0	29
After 30 minutes	0	18	0	28
After 45 minutes	0	28	0	32
After 60 minutes	no contents	20	0	29
Total	0	65	0	118

TABLE 17—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	23	0	23
After 30 minutes	0	26	0	20
After 45 minutes	0	21	0	25
After 60 minutes	0	23	0	25
Total	0	93	0	93

of the Wassermann reaction was negative. Red blood cells numbered 2,300,000, white blood cells 4,000, and hemoglobin 40 per cent. The smear taken showed every symptom of pernicious anemia. Except for evidence of extreme anemia, the remainder of the examination was essentially normal. There was not any fasting contents obtained.

After the administration of atropine, the results of the gastric analysis were as shown in table 16.

After the administration of pilocarpine the results of gastric analysis are given in table 17.

After the administration of epinephrine, gastric analysis was made. The results are shown in table 18.

In this case of pernicious anemia, the gastric cells are totally exhausted and cannot be stimulated to activity, whether the stimulus be a normal one, such as the meat broth, or whether it be reinforced by a drug such as atropine, epinephrine or pilocarpine.

TABLE 18—*Acidity of Contents of the Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	23	0	58
After 30 minutes	0	26	0	30
After 45 minutes	0	28	0	30
After 60 minutes	0	24	0	25
Total	0	101	0	123

TABLE 19—*Acidity of Contents of the Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	25	42	12	74
After 30 minutes	60	77	39	73
After 45 minutes	80	93	60	72
After 60 minutes	52	66	40	52
Total	217	278	153	211

TABLE 20—*Acidity of the Contents of the Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	14	0	12
After 30 minutes	16	27	14	24
After 45 minutes	32	63	62	74
After 60 minutes	47	54	51	63
Total	115	156	127	173

CASE 6—W K, a man, aged 41, complained of pain in the epigastrium, which usually came on from one to two hours after eating. This pain was aggravated by certain foods taken. He did not vomit but had sour eructations. The results of a physical examination revealed tenderness and voluntary rigidity just above the umbilicus, a large dilated stomach and blood in the stool. Roentgen-ray diagnosis was ulcer of the stomach situated near the pylorus. The results of gastric analysis are shown in table 19. Eighty cubic centimeters of the contents of the stomach was aspirated while the patient was fasting, the free hydrochloric acid was found to be 28, and the total acidity 42.

The patient demonstrates the asthenic hyperacid type of secretion.

After the administration of atropine gastric analysis was made. The results are shown in table 20.

Thus, after atropine is given, the type of secretion is nearer that of the normal, although the hyperacidity persists. It has been observed clinically that atropine produces aggravation of symptoms in some cases of gastric ulcer, whereas in others it apparently produces relief from symptoms. This difference of action can be explained by stating that in those cases in which the gastric cells have retained their power of accommodation, atropine, by converting the asthenic hyperacid type of secretion into the normal type, produces relief, but in cases in which the dysfunction has reached a point where conversion of one type to another is no longer possible, atropine either does not have any effect, or else may serve to aggravate the dysfunction.

TABLE 21—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	19	12	23
After 30 minutes	29	50	20	31
After 45 minutes	43	51	17	31
After 60 minutes	38	47	23	43
Total	132	170	112	151

TABLE 22—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	14	22	38	72
After 30 minutes	24	32	52	68
After 45 minutes	42	51	68	76
After 60 minutes	32	45	61	70
Total	112	153	222	266

After the administration of epinephrine, gastric analysis gave the results shown in table 21.

After epinephrine is given there is a decrease in the acidity, but the asthenic type of the secretion remains.

Pilocarpine was next administered. The following results of gastric analysis are shown in table 22.

Here, then, the pilocarpine has converted an asthenic type of secretion into an inert type.

CASE 7—H. F., a man, aged 26, arrived in Detroit from Argentina three days before his first visit to me. While on the boat coming to Detroit he developed jaundice. When first seen, the skin and sclerae were yellow, the urine was dark and gave a positive reaction to bile. The stools were clay colored. The results of a physical examination were otherwise normal. The jaundice gradually disappeared, and the condition was diagnosed as catarrhal jaundice.

The gastric analyses recorded in table 23 were made while the jaundice was still present. Thirty-two cubic centimeters of the contents of the stomach was aspirated while the patient was fasting, the free hydrochloric acid was found to be 15, and the total acidity 36.

This is the hypersecretory-asthenic type of gastric secretion, usually noted in cases of catarrhal jaundice, which indicates that the gastric cells are in a state of irritation and due to this irritation, are approach-

TABLE 23—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	23	40	23	42
After 30 minutes	56	76	51	71
After 45 minutes	68	82	48	68
After 60 minutes	58	72	43	53
Total	205	270	165	234

TABLE 24—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	10	24	34	57
After 30 minutes	28	35	60	72
After 45 minutes	60	75	72	84
After 60 minutes	68	82	58	66
Total	166	216	224	279

TABLE 25—*Acidity of Contents of the Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	4	12	11	21
After 30 minutes	24	30	38	52
After 45 minutes	30	39	60	75
After 60 minutes	33	40	54	66
Total	91	127	163	214

ing the point of fatigue, as may be seen from the decrease in the secretion with the second test breakfast. After epinephrine was administered gastric analysis was made. The results are shown in table 24.

Although, after epinephrine was given, the hyperacidity persisted, the type of secretion approached more closely the normal.

As in the previous cases, pilocarpine was administered. The observations made in this case are listed in table 25.

Pilocarpine has converted a hypersecretory asthenic type of secretion into a normosecretory inert type. One can assume that the pilo-

carpine, reaching irritated gastric cells that were already near fatigue, further depressed their secretory activity by overstimulation. The patient's jaundice did not persist long enough to determine the effect of atropine on his gastric secretion.

CONCLUSIONS

1 Evidence is presented to show that one type of gastric secretion can be converted into a different type of secretion by the use of atropine, epinephrine or pilocarpine.

2 The use of these drugs is suggested as a diagnostic measure in differentiating functional from organic achylia.

3 Since the reserve energy of the cell depends on the functional phase or degree of fatigue of the cell at the time that stimulation is instigated, the use of atropine, epinephrine and pilocarpine furnishes a means of estimating the reserve energy of the secreting gastric cells.

4 An explanation is offered reconciling previous apparently contradictory observations on the action of atropine, epinephrine and pilocarpine on the stomach.

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AREA OF THE BODY SURFACE AND MEASUREMENTS OF THE NORMAL HEART

A PRELIMINARY REPORT

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There has been insufficient study of the measurements of the normal heart. The number of cases of normal hearts measured in men are comparatively few, while the number for women and children are still less.¹ The averages and ranges of measurements are usually given for weight, height, age and diameter of the chest, but, as suggested by Cohn² after a study of his curves and those of Dietlen³ and Schieffer,⁴ in judging the normality of a given heart, it is necessary to have more than a single criterion, such as weight or height. A review of the literature on measurements of normal hearts fails to show any classification of the persons studied in regard to whether they were above, below or of average or ideal weight for the respective height and age.

According to the investigations of Deutsch and Kauf,¹ there is a direct relation between weight and the diameter of the chest. Since both height and weight can be used for the determination of the area of the body surface,⁵ I propose to investigate the possibility of using the area of the body surface as a criterion for judging the normality of a given heart. Not only does body surface area incorporate weight, but there appears to be a relation between this area and the size of the capillary bed. Since the size of the entire capillary bed depends on the size of the body and its organs, as does the area of the body surface, it is reasonable to suppose that a direct relation exists between the area of the body surface and the size of the capillary bed. Also as, quoting

* From the Departments of Cardiology, White Cross Hospital and Children's Hospital

1 Deutsch, Kauf and Warfield. Heart and Athletics, St. Louis, C. V. Mosby Company, 1927, pp. 43 and 36.

2 Cohn, A. E. An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25** 499 (May) 1920.

3 Dietlen, H. Ueber Grosse und Lage des normalen Herzens und ihre Abhängigkeit von physiologischen Bedingungen, Deutsches Arch. f. klin. Med. **88** 55, 1906.

4 Schieffer. Ueber den Einfluss des Militärdienstes auf die Herzgrosse, Deutsches Arch. f. klin. Med. **92** 392, 1908.

5 DuBois, E. F. Basal Metabolism in Health and Disease, p. 143. chart by W. M. Boothby and R. B. Sandiford, Philadelphia: Lea & Febiger, 1924.

from Hershfelder,⁶ "Josue"⁷ has shown, repeated injections of epinephrine in the rabbit are followed by a permanent rise in blood pressure Aubertin⁸ has found hyperplasia of the suprarenals in arteriosclerotic persons, while A. E. Cohn found the same condition in patients without arteriosclerosis Moreover, Fraenkel⁹ found an increase of epinephrine in the blood of only a small percentage of patients with hypertension It therefore seems possible that hypertrophy of the heart and arteriosclerosis may often be the result of a hypersecretion of epinephrine, perhaps also of some other internal secretion Since Hershfelder found that epinephrine causes a constriction of the peripheral vessels and capillary bed⁶ with increased heart effort, while Dale, Laidlaw and Richards,¹⁰ who made experiments with histamine, found a dilatation of the capillaries and a pooling of the blood in the capillary bed and decreased cardiac output, which according to MacKenzie¹¹ is a cause of heart failure, it is reasonable to suggest that there is possibly a closer relation between the area of the body surface and the size of the heart than just the fact that this area incorporates height and weight

In this report I have not used my own figures, but have taken those of the 204 soldiers investigated by Cohn² and the 277 investigated by Smith,¹² making altogether 481 cases studied This material was used because there were complete data as to height, weight, age, etc., for each case In the determination of the area of the body surface, the chart from DuBois³ was used, while in the determination of the ideal body weight, figures commonly used by the insurance companies were employed (table 3)

METHOD

The area of the body surface was computed in each of the 481 cases these were classified into groups with areas of from 1.4 square meters to 1.49 square meters inclusive and so on up to 2.1 square meters, with a range of 0.1 square meter in each group (table 1) The average and range of the measurements of the transverse diameter of the hearts in each group were computed, also those

6 Hershfelder, J. O. *Disease of the Heart and Aorta*, Philadelphia, J. B. Lippincott Company, 1918, pp. 268 and 355

7 Josue, O. *Atherome aortique experimental par injections repetees d'adrenaline dans les veins*, *Compt. rend. Soc. de biol.* **55** 1374, 1903

8 Aubertin and Ambard. *Lesions des capsules surrenales dans les nephrites avec hypertension*, *Bull. et mem. Soc. med. d'hop. de Paris* **19** 175, 1904

9 Fraenkel. *Arch. f. exper. Path. u. Pharmacol.* **60** 394, 1909

10 Dale, Laidlaw and Richards. *J. Physiol.* **52** 110, 1918, **52** 355, 1919

11 MacKenzie, Sir James. *Diseases of the Heart*, New York, Oxford University Press, 1925, p. 26

12 Smith, B. *Teleroentgen Measurements of the Hearts of Normal Soldiers*, *Arch. Int. Med.* **25** 522 (May) 1920

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Height in 481 Cases Classified in Groups

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, Kg	Ideal Weight, Kg	Height, Cm	Age
1 47	1 42	13 6	53	47	152	29
1 51	1 46	13 4	53	48	157	21
1 58		12	54		164	40
1 55		11 9	54		162	20
1 54	1 47	12 8	55	49	158	29
1 55	1 47	13 9	56	49	158	25
1 58	1 48	12 3	57	48	160	19
1 55	1 41	12 6	58	46	155	20
1 59	1 50	12 7	58	50	160	28
1 58	1 48	12 4	59	49	160	24
1 65		13 8	56		173	24
1 64		12 3	56		171	27
1 62		11 2	56		168	22
1 63		12 6	57		168	24
1 66		11 5	57		172	26
1 61		11 2	57		165	23
1 61	1 53	12 8	58	51	163	24
1 64		11 4	58		168	25
1 65		11 2	58		170	25
1 68		11 5	59		169	21
1 61	1 53	11 5	59	53	166	25
1 65		12 5	59		167	23
1 69		12 4	60		177	25
1 62	1 52	13 3	60	51	162	24
1 64	1 56	13 3	60	53	164	29
1 68		12 5	60		170	24
1 68	1 50	12 8	61	50	161	27
1 69	1 61	10 5	61	55	168	29
1 62	1 55	13	61	53	164	25
1 65	1 52	11 2	62	51	163	24
1 68	1 57	14 2	62	55	166	30
1 67	1 54	14	63	52	163	33
1 67	1 54	13 5	63	52	163	26
1 68	1 54	12 8	63	52	164	21
1 69	1 55	12	64	53	164	29
1 61		12 1	55		168	27
1 65		11 6	55		173	21
1 60		11 6	55		165	23
1 63	1 53	12 7	57	51	163	24
1 61		11 7	57		165	31
1 62		12 4	57		169	20
1 68		12 5	57		175	20
1 61	1 51	12 6	58	50	163	20
1 65	1 51	12 8	58	50	163	20
1 65	1 54	12 7	58	52	163	30
1 62		12 6	58		165	30
1 64	1 57	12 5	58	52	168	19
1 63	1 55	13 5	59	52	165	23
1 63	1 56	11 5	59	53	165	25
1 63	1 56	12 6	59	53	165	29
1 69		12 8	58		173	23
1 60	1 49	12 4	59	49	160	24
1 63	1 53	12 1	59	51	163	22
1 66		12 6	59		168	24
1 66		12 8	59		168	26
1 67		13 6	59		170	23
1 67		12 7	59		170	23
1 67		12 8	59		170	30
1 69		12 7	59		173	24
1 69		12 9	59		173	27
1 69		12 7	59		173	28
1 69		12 7	59		173	28
1 62	1 47	12 7	61	48	169	20
1 62	1 50	11 9	61	50	169	26
1 64	1 54	10 1	61	52	163	26
1 66	1 55	12 6	61	52	165	24
1 68	1 58	12 8	61	58	168	19
1 68	1 61	12 2	61	55	168	26
1 68	1 61	11 7	61	55	168	23
1 68	1 61	12 5	61	55	168	30
1 69	1 62	11 4	61	55	170	23
1 69	1 63	12 7	61	55	170	23

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, Kg	Ideal Weight, Kg	Height, Cm	Age
1 60		137	62		157	25
1 65	1 54	129	62	52	163	26
1 69	1 60	115	62	54	168	22
1 69	1 61	132	62	55	168	25
1 69	1 61	131	62	55	168	28
1 60		113	63		155	26
1 64	1 49	118	63	50	160	30
1 67	1 54	114	63	52	163	27
1 69	1 48	120	67	49	169	22
1 70		127	60		172	25
1 70		127	59		175	19
1 71		113	60		174	20
1 77		125	60		185	25
1 71		108	60		171	21
1 70		125	60		172	23
1 72		118	61		174	24
1 73		117	61		176	27
1 73		119	62		172	29
1 71		123	62		171	26
1 73		125	62		173	25
1 71		12	62		170	20
1 74	1 64	128	63	55	172	50
1 75		138	62		174	40
1 71	1 61	135	62	55	169	21
1 71	1 63	12	63	56	169	28
1 77		127	62		178	23
1 72	1 62	113	63	55	170	23
1 72	1 65	105	62	56	172	20
1 71	1 60	114	64	55	167	30
1 70	1 59	118	63	54	167	24
1 76		128	64		174	23
1 71	1 60	127	64	55	167	31
1 75	1 67	134	64	57	173	24
1 78		122	64		176	21
1 71	1 59	125	64	54	167	24
1 74	1 64	128	64	56	171	26
1 72	1 61	132	64	55	168	23
1 79		142	65		177	28
1 78		132	65		175	28
1 73	1 57	128	65	52	168	20
1 74	1 61	118	65	54	170	20
1 78	1 72	128	65	59	176	21
1 70	1 56	123	65	52	164	17
1 76	1 67	128	65	58	172	27
1 74	1 63	127	65	55	170	23
1 74	1 62	112	65	54	170	20
1 72	1 55	116	65	52	165	22
1 71	1 56	135	66	53	164	27
1 73	1 61	124	66	55	167	26
1 71	1 56	126	66	52	165	21
1 70	1 49	145	67	50	161	25
1 79	1 69	146	67	58	172	29
1 74	1 60	137	67	55	167	25
1 74	1 60	144	67	55	167	26
1 75	1 61	14	67	55	168	27
1 76	1 62	132	67	56	169	23
1 77	1 63	15	67	55	170	24
1 76	1 57	135	68	52	167	49
1 78	1 63	15	68	55	171	24
1 78	1 63	134	68	55	171	21
1 77	1 63	138	68	56	170	26
1 77	1 59	129	69	54	167	22
1 78	1 63	148	69	56	169	26
1 78	1 60	15	71	55	167	26
1 78	1 56	124	72	52	165	23
1 71		124	58		178	23
1 71		118	58		178	24
1 73		125	58		189	24
1 72		129	59		175	19
1 72		128	59		175	21
1 72		127	59		175	27
1 72		128	59		175	30
1 72		123	59		178	32

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Height in 481 Cases Classified in Groups—Continued

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, Kg	Ideal Weight, Kg	Height, Cm	Age
172		12.5	59		178	27
172		14	59		178	30
172		12.7	60		175	23
171		12.1	61		173	20
171		13.1	61		173	22
171		13.2	61		173	23
171		11.6	61		173	24
173		11.3	61		175	19
173		10.6	61		175	22
173		11.2	61		175	22
173		11.8	61		175	23
173		12	61		175	27
175		12.4	61		178	20
175		11.6	61		178	21
175		12	61		178	23
175		12.4	61		178	30
177		12.8	61		180	23
177		12.1	61		180	24
177		11.8	61		180	30
170	1.64	11.4	62	56	170	26
172	1.66	11.1	62	56	173	19
174		12.6	62		175	24
175		11.8	62		178	22
176		12.2	62		178	23
176		11.1	62		178	28
176		12.6	62		178	29
170	1.60	12.1	63	54	168	23
170	1.61	11.8	63	55	168	26
172	1.62	11.5	63	55	170	22
172	1.62	13.6	63	55	170	23
172	1.62	11.7	63	55	170	23
172	1.62	11.7	63	55	170	24
174	1.66	13.2	63	56	173	20
174	1.67	11.2	63	57	173	22
174	1.67	11.6	63	57	173	23
174	1.67	11.8	63	57	173	23
174		11.5	63		173	25
174		12	63		173	25
174		12.7	63		173	26
174		12	63		173	28
175		10.6	63		175	22
175		11.1	63		175	27
175		11.4	63		175	27
178		11	63		178	19
178		12.2	63		178	23
178		11.1	63		178	24
178		12.9	63		178	25
178		12	63		178	27
178		12.1	63		178	28
172	1.57	11.7	64	57	168	20
172	1.60	12.6	64	54	168	22
173	1.62	12.3	64	55	170	21
173	1.62	11.7	64	55	170	23
173	1.62	12.6	64	55	170	24
175	1.67	12.4	64	57	173	21
175	1.67	12	64	57	173	24
177		12.7	64		175	23
177		12.6	64		175	26
177		12.4	64		175	26
179		12.8	64		178	23
179		12.4	64		178	25
179		13.1	64		178	25
179		12.3	64		178	26
170	1.58	12.6	65	52	165	23
172	1.60	13.2	64	54	168	23
172	1.61	13.2	65	55	168	27
174	1.62	12.8	65	55	170	22
176	1.65	13.1	65	56	173	19
176	1.68	12.6	65	58	173	25
176	1.68	13.4	65	58	173	26
178	1.70	12.5	65	58	175	20
178		13	65		175	26
175	1.62	13.7	66	55	170	23
175	1.60	13.4	67	54	168	24

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, Kg	Ideal Weight, Kg	Height, Cm	Age
175	161	136	67	55	168	26
175	161	128	67	55	168	29
176	163	136	67	56	170	23
176	163	126	67	56	170	26
179	160	129	67	58	173	23
173	156	13	68	52	165	22
176	161	139	68	55	168	26
178	161	133	68	54	170	20
178	162	134	68	55	170	22
178	161	135	69	55	169	27
178	161	136	69	55	168	31
179	162	129	69	55	170	21
179	162	135	69	56	170	26
179	161	135	70	55	168	27
181		112	64		181	29
184		122	66		182	25
182		123	66		179	19
181	173	137	67	69	170	27
181	171	124	67	59	175	23
181	172	124	67	69	175	28
181	171	128	68	59	175	24
180	168	118	68	58	174	18
180	169	128	68	54	174	20
181	172	11	68	60	175	20
183	171	121	68	59	176	23
184	174	13	68	61	178	23
182	171	157	69	59	175	42
186		127	69		180	26
182	171	158	69	60	174	31
184	171	126	69	61	177	23
184	175	118	69	62	177	25
188		128	69		182	28
180	164	148	69	56	171	30
184		121	67		180	27
180	166	138	68	56	173	18
180	169	134	68	58	173	25
180	169	127	68	58	173	30
181	172	133	68	60	175	26
183	175	137	68	61	178	24
183		134	68		178	20
185		134	68		180	20
187		136	68		183	40
181	168	136	69	58	172	26
184	175	122	69	62	177	28
186		123	69		180	26
183	171	135	70	60	174	31
187		12	70		180	30
181	164	138	70	56	171	30
184	172	15	70	59	176	40
184	173	133	70	60	176	29
180	164	139	70	56	170	25
184	171	13	70	59	175	24
184	171	118	70	59	175	22
184	170	13	70	58	175	18
182	166	137	71	57	172	22
180	161	14	71	55	169	36
181	164	142	71	56	170	29
186	175	133	71	62	177	34
184	168	14	71	58	172	27
187	175	121	71	61	178	33
184	166	113	71	57	172	23
189	179	127	72	63	179	24
180	159	142	72	54	167	24
185	170	14	72	59	174	22
188	175	13	72	61	178	24
185	169	124	72	58	174	20
185	171	147	72	60	174	20
187	175	134	72	62	177	26
184	167	128	72	57	173	21
185	168	115	73	58	173	25
189	175	141	73	61	178	21
188	171	141	74	60	174	28
182	156	146	74	52	166	22

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, Kg	Ideal Weight, Kg	Height, Cm	Age
1 85	1 62	13 7	74	55	171	24
1 86	1 66	12 3	74	59	172	23
1 86	1 68	13	74	58	172	25
1 89	1 71	14 7	75	60	175	25
1 85	1 64	13 2	75	56	170	28
1 88	1 68	16	75	58	173	25
1 87	1 68	12	75	58	172	25
1 82	1 56	13	75	53	165	27
1 89	1 72	13 2	75	60	175	30
1 88	1 70	12 7	75	59	174	21
1 89	1 71	11	75	59	175	24
1 80	1 80	13 7	64		180	23
1 80		13 8	64		180	26
1 80		13 3	64		180	27
1 86		13 6	67		183	31
1 80	1 67	13 5	68	57	173	22
1 80	1 68	13 6	68	58	173	25
1 81	1 72	11 9	68	60	175	25
1 81	1 72	12 7	68	60	175	26
1 83		13 4	68		178	27
1 83		13 6	68		178	29
1 88		13 6	68		184	28
1 81	1 69	13 6	69	58	173	29
1 82	1 70	12 7	69	58	175	20
1 84	1 75	13 5	69	61	178	21
1 84	1 75	11 4	69	61	178	24
1 86		12 9	69		180	23
1 86		13 1	69		180	26
1 80	1 62	13 5	70	55	170	22
1 82	1 67	13 5	70	57	173	22
1 83	1 71	13 5	70	59	175	23
1 83	1 71	13 4	70	59	175	24
1 83	1 72	13 5	70	60	175	25
1 83	1 72	13 4	70	60	175	28
1 83	1 72	13 5	70	60	175	28
1 83	1 72	13 6	70	60	175	28
1 85	1 75	13 4	70	61	178	22
1 85	1 75	13 3	70	61	178	23
1 85	1 75	13 6	70	61	178	23
1 85	1 75	13 4	70	62	178	25
1 85	1 75	13 4	70	62	178	31
1 85	1 75	13 3	70	62	178	34
1 80	1 60	13 5	71	54	168	24
1 81	1 64	13 4	71	56	170	27
1 81	1 64	13 7	71	56	170	27
1 83	1 68	11 6	71	58	173	26
1 83	1 68	13 5	71	58	173	29
1 85	1 71	12 9	71	59	175	21
1 84	1 72	13 3	71	60	175	26
1 84	1 72	13 4	71	60	175	32
1 87	1 75	13 4	71	62	178	27
1 87	1 75	13 6	71	62	178	28
1 87	1 75	13 4	71	62	178	29
1 87	1 75	13 2	71	62	178	30
1 88	1 81	13 4	71	62	180	28
1 81	1 61	13 4	72	55	168	30
1 82	1 64	13 8	72	56	170	26
1 85	1 67	13 5	72	57	173	24
1 85	1 68	13 4	72	58	173	28
1 86	1 71	13 7	72	59	175	21
1 88	1 75	13 5	72	61	178	24
1 83	1 64	13 7	73	56	170	26
1 83	1 64	14 2	73	56	170	32
1 87	1 72	13 5	73	60	175	25
1 89	1 75	13 4	73	62	178	26
1 80		12 9	65		178	36
1 81		11 4	65		180	23
1 81		13 3	65		180	27
1 84		13 7	65		184	23
1 84		12 8	65		184	28
1 81		12 9	66		178	23
1 81		12 2	66		178	26
1 82		13 6	66		180	26
1 82		13 6	67		178	21

TABLE 1—Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued

Actual Surface Area, Sq Meters	Ideal Weight Surface Area, Sq Meters	Transverse Diameter, Cm	Actual Weight, kg	Ideal Weight, kg	Height, Cm	Age
1 82		12 9	67		178	23
1 82		13 5	67		178	23
1 82		13	67		178	31
1 84		13 4	67		180	24
1 80	1 53	13 7	75	52	163	31
1 84	1 66	13 9	75	51	168	23
1 88	1 68	13 7	75	58	173	28
1 88	1 68	13 6	75	58	173	29
1 85	1 60	13 7	76	54	168	23
1 89	1 67	13 6	76	57	173	23
1 84	1 55	14 3	77	52	165	23
1 86	1 61	13 7	77	55	168	26
1 89	1 64	13 7	79	56	170	25
1 88	1 56	13 5	81	53	165	26
1 90		12 8	70		184	27
1 91	1 75	13 3	74	62	178	27
1 96		12 7	74		186	23
1 91	1 72	11 5	76	60	176	25
1 94	1 80	12 3	77	61	179	28
1 96	1 82	12 8	77	61	181	30
1 90	1 67	14 2	78	59	175	24
1 90	1 83	12 3	71	61	183	19
1 90	1 80	13 3	72	61	180	29
1 90	1 80	13 6	72	61	189	31
1 92		13 5	72		183	25
1 93		13 8	72		184	25
1 93	1 81	13 5	73	66	183	30
1 90	1 74	13 7	74	61	178	23
1 91	1 75	13 5	74	62	178	28
1 92	1 79	13 8	71	63	189	21
1 92	1 80	13 8	74	61	189	27
1 92	1 80	13 9	71	61	189	30
1 94	1 84	13 8	74	65	183	31
1 92	1 71	13 5	75	61	178	24
1 92	1 75	13 9	75	62	178	24
1 93	1 79	13 5	75	63	180	24
1 93	1 80	13 5	75	64	180	26
1 93	1 80	13 6	75	64	180	26
1 93	1 80	13 8	75	64	180	30
1 93	1 80	13 7	75	64	180	31
1 96	1 88	13 7	75	68	184	27
1 96	1 88	13 5	75	68	184	28
1 93	1 74	13 4	76	61	178	23
1 93	1 75	13 5	76	62	178	31
1 94	1 79	13 8	76	63	180	23
1 94	1 80	13 7	76	61	180	29
1 94	1 80	13 7	76	61	180	29
1 97	1 82	13 6	76	63	184	25
1 90	1 68	13 8	77	58	173	25
1 90	1 68	13 4	77	58	173	28
1 91	1 72	13 8	77	60	175	25
1 94	1 74	13 7	77	61	178	24
1 94	1 75	13 6	77	62	178	27
1 95	1 80	13 4	77	61	180	27
1 91	1 68	14	78	58	173	26
1 95	1 75	13 5	78	62	178	27
1 95	1 71	14 2	79	60	178	29
1 99	1 84	13 2	79	66	185	25
1 97	1 75	13 9	80	62	178	25
1 98	1 80	13 5	80	64	180	30
1 98	1 75	14 3	81	62	178	28
1 99	1 80	13 3	81	64	180	30
1 95	1 68	13 5	82	58	173	25
2 01	1 80	14 3	84	64	180	27
2 02	1 83	12 5	83	65	182	21
2	1 80	13 8	83	64	179	23
2 04	1 80	13 8	86	64	180	26
2	1 88	13 5	79	68	184	25
2	1 75	13 8	83	62	178	25
2	1 75	13 6	83	62	178	29
2 08	1 87	13 7	84	67	184	38

for persons of ideal weight and those for persons with above-ideal weight, and a comparison was made (table 2). A variation of 10 per cent was allowed before classification as above or below ideal weight (table 3).

The above-ideal weight cases were subdivided into subgroups according to what the area of the body surface would have been, if the weight had been ideal. These figures were compared with averages and limits of transverse diameters in all the groups, in the ideal weight group and in the entire above weight groups, they were also compared with each other (table 4).

TABLE 2—Average and Range of Heart Measurements of Each Group

Surface Area Group, Sq Meters		Ideal Weight, Cm	Above Ideal Weight, Cm	Entire Group, Cm
1.4 to 1.49	Average Number Limits		13.6 1	12.6 1
1.5 to 1.59	Average Number Limits	11.9 2 11.9 - 12	12.8 7 12.3 - 13.9	12.6 9 11.9 - 13.9
1.6 to 1.69	Average Number Limits	12.3 31 11.2 - 13.8	12.4 40 10.1 - 14.2	12.4 71 10.1 - 14.2
1.7 to 1.79	Average Number Limits	12.2 71 10.6 - 14.2	12.8 81 11.3 - 16	12.5 152 10.5 - 15
1.8 to 1.89	Average Number Limits	12.9 23 11.2 - 13.8	13.3 115 11.3 - 16	12.9 148 11 - 16
1.9 to 1.99	Average Number Limits	13.2 4 12.8 - 13.8	13.6 45 12.3 - 14.5	12.5 49 12.3 - 14.5
2 to 2.09	Average Number Limits		13.6 8 12.5 - 14.3	13.6 8 12.5 - 14.3

TABLE 3—What a Man Should Weigh

Height, Cm	Years									
	19	20	21 and 22	23 and 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 and Over
	Kg	Kg	Kg	Kg	Kg	Kg	Kg	Kg	Kg	Kg
152.5	45	45	46	46	47	47	46	46	45	45
155	46	46	47	47	48	48	47	47	46	46
157.5	47	47	48	48	49	49	48	48	47	46
160	48	48	49	49	50	50	49	49	47	47
162.5	49	50	51	51	52	52	51	50	49	49
165	51	51	52	52	53	53	52	52	51	50
167.5	52	52	54	54	55	55	54	54	52	52
170	54	54	55	55	56	56	55	55	54	53
172.5	56	56	57	57	58	58	57	56	55	55
175	58	58	59	59	60	60	59	59	58	57
177.5	59	60	61	61	62	62	61	60	59	58
180	62	62	63	63	64	64	63	62	61	61
182.5	64	64	65	65	66	66	65	65	64	63
185	66	67	67	68	68	68	67	66	65	65
187.5	68	69	70	70	71	71	70	69	68	67
190	71	71	72	72	73	73	72	71	70	70

Lastly, the curves of the averages and limits of the transverse diameters of the hearts in all the groups, in all the ideal weight groups and in all the above-ideal weight groups were compared with the curves of other investigators Cohn's² and Smith's¹² weight curves (table 5). Smith's¹² and Deutsch, Kauf and Warfield's¹ height curves (table 6). Deutsch, Kauf and Warfield's¹ age curves (table 7).

TABLE 4—Groups the Patients Would Be Classified In if of Ideal Weight for Height, Sq Meters

Groups, Sq Meters		14 to 149	15 to 159	16 to 169	17 to 179	18 to 189
14 to 149	Average, cm	136				
	Numbers	1				
	Limits, cm					
15 to 159	Average, cm	129	127			
	Numbers	6	1			
	Limits, cm	123-139				
16 to 169	Average, cm	124	125	12		
	Numbers	1	27	9		
	Limits, cm	118-129	101-112	105-112		
17 to 179	Average, cm	115	125	129	126	
	Numbers	1	13	65	2	
	Limits, cm		116-135	105-15	125-128	
18 to 189	Average, cm		138	132	132	135
	Numbers		6	47	61	2
	Limits, cm		12-116	113-16	115-17	134-137
19 to 199	Average, cm			137	137	134
	Numbers			5	18	22
	Limits, cm			134-142	133-145	123-139
20 to 209	Average, cm				137	136
	Numbers				2	6
	Limits, cm				136-138	125-143

TABLE 5—Cohn's and Smith's Weight Curves*

Cohn's Cases		Smith's Cases	
Weight, Kg	Transverse Diameter, Cm	Weight, Kg	Transverse Diameter, Cm
53	130	55	119
54	119	56	116
55	128	57	123
56	128	58	125
57	119	59	127
58	118	60	127
59	120	61	120
60	123	62	123
61	119	63	118
62	125	64	126
63	126	65	129
64	127	66	131
65	126	67	131
66	124	68	131
67	137	69	131
68	132	70	135
69	133	71	133
70	131	72	136
71	134	73	137
72	132	74	138
73	143	75	137
74	134	76	136
75	132	77	137
76	145	78	138
77	125	79	137
78	142	80	137
79	135	81	137
80	138	82	135
		83	137
		84	137

* From Cohn, A. J., An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch Int Med 25:504 (May) 1920. Smith, B. Teleroentgen Measurements of the Heart of Normal Soldiers, Arch Int Med 25:525 (May) 1920.

COMMENT

Comparison of the average transverse diameters of hearts in the various body surface area groups shows that for persons of ideal weight (table 2) they are smaller than for those of the above-ideal weight or for the entire group, while the averages of the above-ideal weight and of the entire group are practically the same

TABLE 6—*Smith's and Deutsche, Kauf and Warfield's Height Curves**

Smith's Cases		Deutsche, Kauf and Warfield Cases	
Height, Cm	Transverse Diameter, Cm	Height, Cm	Transverse Diameter, Cm
155	12.0	131-140	20.7
157	13.1	141-150	21.9
160	12.7	151-160	23.3
163	12.2	161-170	24.2
165	12.7	171-180	24.5
168	12.9	181-190	25.5
170	12.9	191-200	25.1
173	13.3		
175	12.6		
178	13.0		
180	13.3		
183	13.5		
185	13.5		

* From Smith, B. Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch Int Med 25: 525 (May) 1920 and Deutsche, Kauf and Warfield, Heart and Athletics, p. 36

TABLE 7—*Kauf and Warfield's Age Curves**

Deutsche, Kauf and Warfield Cases					
Age	Transverse Diameter, Cm	Age	Transverse Diameter, Cm	Age	Transverse Diameter, Cm
10	9.9	19	11.4	28	12.1
11	10.1	20	11.5	29	11.8
12	10.2	21	11.5	30	11.9
13	10.0	22	11.6	31	11.8
14	10.6	23	11.6	32	12.2
15	11.2	24	11.8	33	11.7
16	11.2	25	11.8	34	12.2
17	11.1	26	11.7	35	12.2
18	11.4	27	12.0	36-40	11.8

* From Deutsche, Kauf and Warfield, Heart and Athletics, p. 37

The range between the largest and smallest transverse diameters of the hearts in the ideal weight group is less than in either of the other groups, while it is practically the same in the above-ideal weight group and in the entire group. It would therefore appear that the high averages for the transverse diameter of the heart and the wide range in size in each group were due to those cases in which the weight was above the ideal for the height.

If one compares the curves of ideal weight cases according to body surface area with curves based on height (table 6), weight (table 5) and age (table 7), it will be noted that the rise is more consistent

When one compares the average transverse diameters of the hearts in the above-ideal weight group subdivided according to the body surface area group this group would have been in if the weight had been ideal with the averages in the ideal weight group, it is evident that the averages of the former are greater than of the ideal weight group of the same body surface area (table 8), and that the greater the above-ideal weight the greater is the deviation from the average for the ideal weight (tables 4 and 8)

TABLE 8—*Comparison of Heart Diameters of the Above-Ideal Weight, Classified According to Their Ideal Weight, with Those of the Ideal-Weight Group**

Skin Surface Area Groups, Sq Meters	Ideal Weight Group Transverse Diameter, Average, Cm	Above-Ideal Weight Cases (Subdivided According to the Surface Area Group They Would be in if of Ideal Weight for Height) Averages, Cm
14 to 149		12.9, 12.4, 14.5
15 to 159	11.9	12.5, 12.5, 13.8
16 to 169	12.3	12.9, 13.2, 13.7
17 to 179	12.2	13.2, 13.7, 13.7
18 to 189	12.9	13.4, 13.6
19 to 199	13.2	
20 to 209		

* Only one case in the ideal weight group for skin surface area 14 to 149 square meters therefore this average is not used

TABLE 9—*The Transverse Heart Diameter Averages of the Above-Ideal Weight Group, Classified as of Ideal Weight and Compared with the for Height, Sq Meters**

Skin Surface Area Groups, Sq Meters	Ideal Weight Group Transverse Diameter, Average, Cm	Above-Ideal Weight Cases (But in the Same Skin Surface Area Group as if of Ideal Weight for Their Height) Averages, Cm
14 to 149		
15 to 159	11.9	12.7
16 to 169	12.3	12
17 to 179	12.2	12.6
18 to 189	12.9	13.5
19 to 199	13.2	
20 to 209		

* Only one case in the ideal weight group for skin surface area 14 to 149 square meters, therefore this average is not used

Even the averages of the transverse diameters of the heart in the above-ideal weight subdivisions, which are still in the same body surface area group they would be in if the weight were ideal, are above the averages for the ideal group (table 9)

The largest transverse diameter of the heart for all groups in the ideal weight class is 14.2 cm, the lowest 10.6 cm, while the largest for the above-ideal weight group is 16 cm and the lowest 10.1 cm

Curves representing the transverse diameters of hearts in persons of ideal weight, the area of the body surface being used as a criterion

include the following variables height, weight, age, sex and diameter of the chest, indirectly concerned through its relation to weight

CONCLUSIONS

1 Cases of ideal weight for height should be used in the estimation of the measurements of a normal heart

2 The individual case of above-ideal weight for height gives the greatest variation from the average transverse heart diameter or from the diameters of hearts of ideal weight

3 The curves of average transverse diameters, body surface area being used as a criterion, show the least variation

4 As the area of the body surface as computed also includes other variables, it approaches a clinical criterion for the estimation of the size of the normal heart

Book Reviews

MODERN MEDICAL MONOGRAPHS Edited by HUGH MACLEAN, M.D., D.Sc.,
F.R.C.P., Professor of Medicine, University of London

THE ENDOCRINES IN GENERAL MEDICINE By A. LANGDON BROWN, M.S., M.D.,
F.R.C.P., Physician to St. Bartholomew's Hospital Price, \$3 Pp 134
with index, no reference to the literature and no illustrations New York
Paul B. Hoeber, 1927

This latest endocrine monograph in English is, according to the preface, "chiefly a record of the author's personal experience, first in the laboratory and later with patients." Besides the usual chapters on the individual glands and group of diseases, the author assays prophesy in the last chapter headed by the title "The Future of Endocrines." The thymus and pineal gland are discussed under the heading "The Retarding Glands." The monograph is easily read, the style being pleasing and clear, but the chief merit of the book is its brevity. The author says that his main aim is service to the general practitioner. It is to be regretted that so much unproved theory, speculation, disproved assertions and out and out nonsense should be served out as an aid to the practitioner in medicine who really needs guidance in this difficult field.

The following quotations justify the above stricture. As evidence of the physiologic effects of feeding the anterior lobe of the pituitary, the author cites the following: "Mr. Crossley-Meates has kindly informed me that he gave 2 grains of anterior lobe extract daily to an Irish wolfhound bitch-pup four months old. In a month the facial expression became heavy and the ears large, so that it resembled a bloodhound. The long bones were definitely larger and heavier than those of the rest of the litter. But the most striking difference of all was the change in character, for this bitch-pup would domineer over the rest of the litter, including the dog pups, and at eight months old she was more masculine and rougher in play than they were." This is medicine of 1927 almost at its worst. The following seems more appropriate from a writer of fiction than a guide of medical men: "The pituitary seems to play a special part with regard to rhythmic functions, and on the psychical side to show this in the direction of music and dancing, or on the more intellectual side with mathematical or more imaginative interests, widely as the last two seem to differ."

And what about the following? "A young man of 23 was brought to see me, who had been very late in learning to walk and talk. He showed me two photographs of himself taken at the age of 4 or 5—one of these looked like a normal child while the other looked degenerate. By the age of 6½ he had developed the habit of lying. He grew rapidly to the height of 6 feet 5 inches. His palatal arch was very high and his knuckles were very large. He was a confirmed liar and thief and was suspected of deliberate and wilful arson—the fossa becoming too small for the gland, the patient is apt to develop moral and intellectual inferiority, to suffer from compulsions and obsessions and to lack inhibitions. As Berman puts it, such individuals are 'pathological liars with little or no initiative or conscience.'"

On page 111 the author quotes with apparent approval the speculation that the anterior lobe of the pituitary tends to produce virile characters and the posterior lobe feminine characters and adds this charming bit of evidence: "We are all familiar with the inseparable couple of women friends. One of the two usually adopts a somewhat masculine role, and I have been struck on several occasions to note the number of signs she presents of overactive anterior pituitary."

On page 113 the author states that "persistence of the thymus produces, in addition to status lymphaticus physically," a "mother's darling psychologically."

On the question of testicular transplantation the author quotes Dr Kenneth Walker with approval to the following effect "Up to the present time I (Dr Walker) have performed Steinach's operation on fifteen cases, and although it is difficult to eliminate the element of suggestion I believe that in at least half of these cases an improvement in general health and an increase in mental vigor have taken place. I am particularly inclined to recommend the operation in the treatment of that hopeless malady of later life, paralysis agitans, having seen a very marked improvement in two out of four cases which I have treated in this way. It is frequently advisable to combine testicular grafts with the use of extracts of other endocrine glands, notably of the pituitary, the suprarenals or the thyroid."

The author refers to pituitary extract again and again as a lactagogue, although it was shown many years ago that it has no influence on the production of milk except to retard it when pituitary extract is used in large doses, and despite the growing evidence that the hormone of the parathyroid gland is ineffective when given by mouth, the author persistently refers to the therapeutic effects by giving parathyroid material by mouth. In the same way the author seems to be unfamiliar with much of the work which tends to show that diabetes insipidus is due to injury of the brain and not to hypofunction of the posterior lobe of the hypophysis, and that obesity associated with Frohlich's syndrome is of brain origin and not an index of depression of the function of the anterior lobe of the hypophysis.

After completing the book the reader will have the impression that the author is a charming fellow, disinclined to question or contradict, with little information, and much faith. In view of the general poor and unreliable character of the book, it is surprising to find that the best chapter is (no 11) headed "Endocrine Therapy." To be sure we meet even here such statements as "oral administration of parathyroid extract certainly seems to be effective," and "extracts of the whole pituitary gland should be given in cases of defective growth and development." He puts forth a rather weak argument for pluinglandular therapy but adds at once, "One must admit that pluinglandular therapy is generally irrationally applied."

The author seems most confused in the field of the pituitary gland. On page 64 he says, "Under action of the posterior lobe may lead to general obesity or localized fatty deposits. Of the latter type Dercum's disease—adiposis dolorosa—is a good example. The disease is refractory in treatment, but I have seen decided benefit from thyroid extract together with injections of pituitrin, especially when combined with a suitable diet for obesity." This is not only pluinglandular therapy, it is shotgun therapy. The adipose patient thus treated will probably lose some weight but losing weight on such management does not help us discover the cause of the adiposity. The monograph is not a serious contribution to the theory and practice of medicine. It will be a hindrance rather than a help to the progress of general practice.

THE SIGNIFICANCE OF THE PHYSICAL CONSTITUTION IN MENTAL DISEASE By F. I. WERTHEIMER, Phipps Psychiatric Clinic, and FLORENCE E. HESKETH, Johns Hopkins Hospital. Medicine Monograph Series. Price, \$2.50. Pp. 76 with illustrations. Baltimore: Williams & Wilkins Company.

The authors present a compact discussion of their theme, defining the human constitution for the purpose of their investigation as "the correlative unity of those morphological, physiological and psychobiological developments of the individual which are definitely more influenced by heredity than by environment." Classifications of body types beginning with Hippocrates' "habitus apoplectic" and "habitus phthisic" and leading on up to Kretschmer's athletic, pyknic and asthenic groupings are tabulated and critically discussed.

The material of this study consists of sixty-five male patients chosen at random from the Phipps Institute, Johns Hopkins Hospital and a Maryland state hospital. Psychiatric, observational and anthropomorphic data were not

compared until the final correlation. Classification of morphologic types was made according to Kretchmer's descriptive method.

The authors' research contribution consists of the formulation—after the calculation and analysis of about thirty-seven different mensural indexes in each patient—of an index relating leg length to chest diameters and trunk length

$$\text{Index} = \frac{\text{Leg length } 10^3}{\text{Transverse chest diameter} \times \text{sagittal chest diameter} \times \text{trunk height}}$$

The numerical values thus obtained are charted in a convincing manner to show no overlapping of values thus obtained in clear observation types so far as the pyknic and athletic-asthenic groupings are concerned. The average values for the three types are distinct.

The psychiatric correlations are interesting and demonstrate the value of Kretchmer's work. The authors appear to have made a decided contribution to psychiatry, and mental hygiene, in giving a reliable check on mere observation which is so apt to lead one astray.

A four page bibliography is not the least valuable portion of a brief monograph representing an infinite amount of labor.

KLINISCHE GASSTOFFWECHSELTECHNIK. Von Dr. H. W. KNIPPING, Privatdozent an der Medizinischen Klinik der Universität Hamburg, and Dr. H. L. KOWITZ, Professor an der Medizinischen Klinik der Universität Hamburg. Paper. Price, 18 marks. Pp. 193, with 72 illustrations and 2 tables. Berlin. Julius Springer, 1928.

This is a compact, accurate and useful little monograph on methods of basal metabolic studies for clinical purposes. While the German physiologists, especially Voit and Rubner, were the leaders in establishing the laws of nutrition and metabolism, the practical application of these principles in the clinics was essentially perfected and applied in the United States, and there are several monographs in English dealing with this subject. The present volume, therefore, presents to English readers nothing essentially new on the subject, except in the way of a model of compact and accurate presentation. Various European apparatus are described that are not in general use in this country, but these apparatus do not appear to have a great advantage over those in common use in this country. The appendix contains the necessary tables and charts for rapid calculations.

QUESTIONS PHYSIOLOGIQUES D'ACTUALITE. LEON BINET, Professeur agrégé de Physiologie à la Faculté de Médecine de Paris. Paper. Price, 18 francs. Pp. 227, with 57 illustrations. Paris. Masson & Cie, 1927.

This monograph contains twenty-four chapters or lectures given as conferences on problems in physiology in the medical faculty of the University of Paris during the year 1925-1926. It is in no sense a textbook or monograph covering the whole aspect of physiology, but the author has taken a number of problems, such as sleep, tobacco, the spleen, cerebral circulation and others and has developed the present status of these problems in the light of experimental and clinical data. It is well written and concise, but in many cases superficial, discussion of many problems that are important in both fundamental physiology and medicine. Some of the chapters or lectures refer to the fundamental or important literature on the subject.

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EPIDEMIC ENCEPHALITIS

AS OBSERVED AT THE FIRST CZECH MEDICAL
CLINIC IN PRAGUE

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The infectious disease with which our article deals does not seem to be new in the medical world it is quite certain that it appeared from time to time as an endemic many centuries ago There are authors (Netter) who think that Hippocrates knew about its peculiar aspect Nevertheless there is no doubt that the pandemic of epidemic encephalitis which lasted from 1916 up to the present time is the most extensive incidence of this disease

We do not intend to go into a detailed description of the disease since the first reports of Cruchet, Mouttier and Calmette in France and Economo in Vienna in 1917, an enormous bibliography on the subject has appeared There are even many monographs about it (Achard, Reys Mlle Lévy, Conos, Verger and Cruchet, Houn in France, Ministry of Health Hall in England, Timme in the United States, Margulis in Russia and many others)

The first sporadic cases in our country occurred in 1918 They entirely escaped medical observation during their acute form but we discovered their existence in our clinic retrospectively while studying several cases in the chronic form

The epidemic of encephalitis began here at the end of 1919 its appearance was announced for the first time at the meeting of the "Purkyně Medical Society" on Jan. 17, 1920, by Professor Heveroch and one of us (L S¹): the Czechoslovakian bibliography about it dates from here Czechoslovakian neurologists and psychiatrists had a great opportunity to study the disease, as our country seems to have been gravely attacked by it Although official statistics have not yet been made we can say that the number of patients is relatively much higher than for other countries for at least one person in a thousand was affected during these nine years and about ten thousand or more had the disease

We do not wish to and cannot describe, even briefly, the epidemic in our country. Our medical publications concerning it are many. All medical, neurologic and psychiatric clinics published material and their point of view concerning it. In addition to this material and the publications from our institute, the work we cited of Professors Heveroch, Pelnáň, Haškovec, Mysliveček, Bidlík and their pupils. The anatomic observations were made by Docents Šíkl and Krákora.

In this publication, we report only what we saw at the first Czech medical clinic, especially such facts as we hope will comprise an original contribution to the general knowledge of this epidemic disease. We have omitted almost every fact that is accepted as classical.

We saw about one thousand patients affected with encephalitis at the clinic and in consultation. Several hundred patients were observed for months and for years. The greater number of the patients were seen only while they were in the chronic stage. It was only by the number of later manifestations that we could estimate the real extent of the epidemic.

NOMENCLATURE

Conos's term "*neurosystemitis epidemica*" would appear to be the most logical name to employ. No part of the nervous system was found unaffected by the disease. In 1920, one of us (L. S.) expressed in lectures a point of view that at a much later date was confirmed generally, namely, that not only is encephalitis present but sometimes also myelitis, radiculitis and polyneuritis. Nevertheless, we use the term encephalitis only because of the great prevalence of alterations of the brain and because we do not like the term *neurosystemitis* for philologic reasons. The name "*encephalitis epidemica*" is much more suitable than the original term "*encephalitis lethargica*," lethargy not being a constant symptom, thus, ever since the first outbreak of the epidemic (January, 1920) we have used the name *encephalitis epidemica*.

SEASONAL INCIDENCE

We did not have any cases that began in the months of June, July or August. All the cases we saw from 1919 to 1925 began in the other nine months. We stress that point because there is no satisfactory explanation for it. It cannot be explained by the occurrence of catarrh, especially a nasopharyngitis which could readily facilitate the penetration of the virus through the altered mucous membrane. Such catarrh occurs all the year round, at least in isolated cases, but the increased number of cases during the colder months of the year was a constant fact during the six years of our observations.

More than 90 per cent of the cases had their onset in November, December, January, February and March, more than 5 per cent began in January and February. The first great epidemic occurred in January, 1920.

SEX AND AGE

We have not observed that the condition has predominated in either sex

As regards age, we noticed the greatest incidence between the ages of 6 and 36 years. Old persons seem to be the most resistant to the infection, none of our patients were afflicted after the age of 60

DISPOSITION

Many patients presented a pronounced nervous degeneration—a terrain which could give the impression of disposition. Many patients were children of syphilitic parents, members of families in which were several cases of psychosis, alcoholism and hysterical constitution. In some patients, the disease began after a period of hard physical or mental exertion (beginning soon after a party or during the time of examination). More than two thirds of the men who had encephalitis did not smoke, this point is significant if we consider the small percentage of men who do not smoke in our country

CONTAGION

In our large quantity of material, we noted but two suspicious instances. 1. We observed a typical encephalitis-parkinsonian syndrome in the case of a young married couple, both gave the history of a pronounced acute phase, one being attacked several weeks before the other. 2. A woman physician who had as a patient another woman physician who was afflicted with encephalitis also developed a typical case of encephalitis several weeks later. Such a case of apparent infection occurs so seldom that a simple coincidence cannot be excluded.

On the contrary, the epidemic hiccup which we class under a "forme fruste" of myoclonic encephalitis often shows that it is undoubtedly contagious.

THE ACUTE STAGE OF EPIDEMIC ENCEPHALITIS

Classification—We are against any strict cataloging of different forms. The same patient may pass through all the "forms" which have been described, and it is therefore better to speak about the condition of the patient on certain days than about the form of his disease.

One may class the clinical aspects in the great majority of cases under two syndromes: the oculolethargic (of the French school) and the alcohylhyperkinetic. It is unnecessary to point out that even these two primary groups of symptoms may manifest themselves in the patient on one and the same day. The disease is exceedingly multiform in its symptoms and in its evolution.

The mode of onset varied a great deal; many of the patients could not state their first symptoms on account of amnesia during the long period of the acute stage.

When the beginning could be carefully followed, we observed some general prodromes lasting for several days or weeks. It took several days or a few weeks before the clinical aspect of the acute stage developed. Often the precise day of the onset could be given. The first signs varied a great deal. A condition of sleeping (drowsiness or night delirium and insomnia), diplopia, excitomotor phenomena or a nonsystematized vertigo were the most frequent initial symptoms. The ambulatory cases also began with sleepiness, diplopia and often "neuralgic" pains, trigeminal neuralgia, headache and pain in the limbs.

In some cases, encephalitis was preceded by sore throat, pharyngitis, catarrhs of the bronchi and even by bronchopneumonia. That period is not considered as specific by many authors (Levaditi).

Gastro-intestinal symptoms seldom occurred at the beginning, nevertheless, we saw some chronic cases (which during the acute stage were in other services) mistaken for typhoid and paratyphoid fever.

General Symptoms—Fever was usually present, but not always. We shall not describe the fluctuations of temperature in detail. It is well known that symptoms in various cases differed widely. High fever (from about 39 to 40 C [102.2 to 104 F]) was frequent only during the first year of the epidemic (1919 to 1920), later it was exceptional. A high fever always indicated a serious prognosis. It was present in all but one of our fatal cases. The elevation of the temperature always paralleled the general state of the patient. We are not, therefore, inclined to consider the fever a localizing sign in any case (condition of the heat center). Fevers from about 39 to 40 C (102.2 to 104 F) never lasted more than ten days. Subfebrile temperatures of from 37 to 38 C (98.6 to 100.4 F) were often obstinate, and they often continued for weeks. There did not seem to be any fever in some ambulatory cases.

The Symptom of Sleeping—We observed this symptom in every case, except in several ambulatory cases and in cases of epidemic hiccup. Drowsiness with periods of delirium, particularly at night, was the most frequent type of symptom. This association of wakefulness and delirium at night with somnolence or lethargy during the day, especially in children, was a characteristic sign. Many patients suffered only from insomnia, and drowsiness or lethargy could not be noticed during the disease.

Localizing Signs—*Ocular Signs*. Ocular symptoms were frequent, nevertheless, we had some grave cases, especially algomyoclonic, of long duration, in which there were long periods of delirium and in which there was no ocular disorder. The third nerve was most frequently involved. Paralysis was seldom complete. Ocular paralysis in the acute stage was usually of the peripheral type. Only the paralysis of convergence was frequently seen in the acute stage.

We observed all types of disorders of the pupils. Loss or paresis of the reaction of accommodation was the most frequent, in most cases, this loss of reaction was regularly accompanied with paresis of convergence.

Next to the oculomotor nerves, the seventh and the twelfth were most frequently attacked, we saw both the irritative and the paretic phenomena.

We did not observe any disorder of the sensory nerves. All other cranial nerves were often attacked. Vestibular disorders of central type occurred frequently but not constantly. Among the vestibular signs, spontaneous nystagmus seems to be the most frequent.

Bulbar and pseudobulbar pictures were not exceptional, one of us (L. S.) noted them on many occasions (in the first week of the epidemic in 1920²). The evolution of the bulbar symptomatology used to be dramatic. Such a serious condition sometimes takes the patient by surprise when he is in perfect health. The clinical aspect resembles that of poliomyelitis infectiosa acuta. In 1920, one of us (L. S.) emphasized the resemblance of the two diseases when the prevalence of lesions is anatomically confined to the same territory of nerve nuclei of the brain in the subependymal layer of the brain stem.

We had two cases of a complete myasthenic pseudobulbar type, both patients died in a short time, and the diaphragmatic movements were unimpaired in both cases (roentgen-ray control).

Physiognomy. The physiognomy was almost always changing, hypomimia was more frequent than hypermimia.

Typical marked pyramidal hemiplegia was rare, we saw only one case in which this was present. The onset of hemiplegia was apoplectic in the second month of the acute stage, this apoplexy was accompanied by unconsciousness and clonic movements and in the later stage by paralysis of the limbs. Later, in the chronic stage, this hemiplegia was associated with a parkinsonian syndrome.

Excitomotor Phenomena. Rhythmic myoclonus was the most frequent symptom, the zone of predilection for myoclonus being in the abdominal muscles. Myoclonus was frequent, especially in cases in which there was high fever, an association which occurred frequently only during the first year of the epidemic (1920). Later we saw it only a few times. Chorealike movements and fine tremors were not rare, we have not seen the bradykinetic movements in the acute stage. Athetotic phenomena were not observed at all. Excitomotor phenomena, when present, never disappeared while the patient was sleeping. We cannot understand the contradictory statements of other observers.

² Syllaba. Čas lékař čes., Oct 21, 1920, no 12, 31, Čas lékař čes. 61:417, 1922.

Excitomotor phenomena in encephalitis, in that respect, are a great exception from the general semiologic rule

Rigidity of extrapyramidal type was present, especially in the excitomotor stage. This rigidity of extrapyramidal origin may interfere in an interesting way with the peripheral paretic phenomena, especially in the face

Catatonia, particularly the "fictive cushion," was present almost in every case which was not ambulatory

Reflexes. The changes in the tendon and periosteal reflexes were not of a special nature. Irritative pyramidal phenomena were often found during the acute stage. Pussep's reflex was almost constant, and the reflexes of posture (Forn and Thévenard) were almost constantly augmented (Henner)

Meningitic phenomena were not common. Clinically, they were sometimes pronounced in the first days of the disease, but they were always fugitive

Disturbances of the Spinal Cord. We noted some cases in which quadriplegia or spastic paraplegia was present which probably did not originate in the cerebrum. The hiccup is explained by many authors by a lesion in the cervical cord, though a bulbar origin is also probable

Mental Disturbances. Mental disturbances were frequent and varied. The resemblance in some cases to delirium tremens was striking (zoopsia was especially frequent), delirium and hallucinations were exceptional after 1920

Other Disturbances. We have seen the same disorders of the *circulatory and respiratory* systems that the majority of other observers have seen. Even in the acute stage, the dyspnea had different aspects and it differed in origin (Syllaba, 1920³). The bulbar type was the most frequent (we saw also the Cheyne-Stokes type). The two patients with fatal myasthenic cases presented a well marked and increasing fatigue of the respiratory muscles. On the other hand, the dyspnea was often caused by the rigidity of the respiratory muscles. Myoclonus of the abdominal muscles did not seriously embarrass the respiration. Plain bradypnea and tachypnea (as high as 44) were also frequent. The respiration of other patients was of a type that is well known in respiratory neuroses, one deep inspiration from time to time without any relief to the patient. Facial herpes, especially labialis, were rare, we saw herpes zoster in only one of our cases

Polyuria was seen during the acute stage in several cases

The association with bronchopneumonia did not seem to be more frequent than in other serious infectious diseases, nevertheless, it was usually a serious complication. Only two of our seven patients who

died during the acute stage had not had pneumonia. Bronchopneumonia can precede the onset of the nervous symptoms, but in most of our cases it was secondary. The cause of bronchopneumonia could rarely be ascribed to aspiration. Many patients with this complication previously had a slight fever, but they did not show pronounced mental changes nor paralysis of the last brain nerves (Syllaba⁴). A relapse sometimes occurred in this complication, some patients were able to endure the bronchopneumonia surprisingly well and did not present any general alterations, although the physical symptoms were marked.

The Cerebrospinal Fluid. Our observations are in accord with those of other authors. Marked changes were found usually only during the first days, during the meningeal reaction. Hyperglycorrhachia was often present. This is an important point in its differential diagnosis from meningitis, especially when the rest of the symptoms would suggest meningitis (increased pressure, cell count and protein content). Hypoglycorrhachia, however, does not exclude encephalitis. Červenka found a sugar content of only 0.03 per cent in several cases.

The changes in the scope of the epidemic in our state could be well followed at our clinic. The greatest epidemic occurred during the winter of 1919 to 1920. During the winter of 1920 to 1921 far fewer cases of encephalitis occurred and from 1921 to 1922, the epidemic was still milder, during the winter of 1922 to 1923, however, there was a distinct recrudescence, the epidemic being more widespread than it had been since the winter of 1919 to 1920,⁵ from 1923 to 1924 the fewest cases appeared. During the year 1924 to 1925 we saw only nine new cases. The last acute form we saw (up to October, 1927) was in October, 1925. The hibernal revival of encephalitis was preceded every year by a short epidemic of epidemic hiccup; as we remarked before, that form apparently is contagious. It may be that the persons with hiccups are the propagators of encephalitis.

The gravity of the acute stage diminished from year to year. Deaths occurred in the acute stage only in 1920 (9.2 per cent, seven in seventy-six⁶), no patient died in the acute stage of the condition after April, 1920. It is almost certain that the treatment, which is today more systematic than in 1920, plays a certain rôle in the decrease of mortality, but there is no doubt that the whole clinical picture became much lighter from year to year after 1920, and a temperature higher than 38°C became exceptional. Myoclonus, as we have already said, became rare. Mental symptoms became less serious and marked delirium was seen in only one case after 1920 (in 1923), the duration of the acute stage was also much shorter.

4 Syllaba Čas lék čes., 1922, no. 6

5 Henner Čas lék čes. 62:664, 1923

6 Labohy Sborn lék., 1923, p. 258

THE CHRONIC STAGE

The majority of our patients were studied only while they were in the chronic stage of the condition. It was not until after several years that we realized the enormous extent of the outbreak of the endemic of encephalitis during 1919 to 1920. The great number of cases and the peculiarity of the chronic form were the greatest surprise in this disease.

We have not seen a case of contagion in the chronic stage, although our patients were not isolated and though scarcely any prophylactic measures were taken.

Nomenclature—The greater number of cases in the chronic stage were progressive and evolutionary, only a small number were stationary. We have not seen any chronic cases which were spontaneously regressive. Patients on whom physical examinations were made during the chronic stage of the disease by other authors always showed fresh inflammation among other symptoms. For these reasons we do not accept the terms "status postencephaliticus," "chronic residua," "sequelae" ("postumi") and prefer the more suitable term *encephalitis epidemica chronica*.

The clinical aspect of the chronic stage varies much, nevertheless, it does not vary as much less as in the acute stage.

The parkinsonian syndrome is the most frequent and the most prevalent. In every other form of the chronic stage, parkinsonian elements were always found and usually represented its latest aspect, even in cases in which the chronic stage began with another picture. All cases of chronic encephalitis end in the parkinsonian syndrome, the sole exception in our cases was that torsion spasm sometimes developed after a parkinsonian syndrome.

Mode of Onset—1. After the disappearance of the general symptoms—fever, lethargy or insomnia with delirium, headache—and the greater part of the localizing signs, many patients begin to walk about, but recovery is not complete, their movements are slow, and the changes in physiognomy and the excitomotor phenomena may persist for a short time. This is a prolonged form of the acute stage which gradually changes into the chronic stage, usually into the parkinsonian syndrome.

2. Many patients present an interval of apparently complete recovery.⁷ They feel well, and they do their work as well as before the illness. This period may last a long time. We had cases in which such a period of latency lasted five years. One must concede that

⁷ Syllaba Čas lék čes 61 417, 1922

this period might be still longer in some cases, it is one of the reasons why it is so difficult to speak about a complete recovery in any case of encephalitis

3 The third category is also a special one. There are patients who develop the chronic form of encephalitis without knowing that they have had an acute form. If asked concerning their symptoms, they answer that some years ago they were a little sleepy, or that they could not sleep for a time, for several days they had diplopia, but not continuously, all clinical manifestations were so slight that they were not obliged to seek medical aid.

We may say that there is no correlation between the gravity of the acute and of the chronic stage. After a serious acute stage there may come a serious chronic manifestation, but this may also follow an ambulatory or a "fruste" acute form. On the other hand, the patient with the most severe and the most prolonged acute form may recover completely and not have a recurrence (up to the present, we may say only for seven years).

The First Objective Signs of a Parkinsonian Syndrome—In the majority of cases, the first symptoms are to be seen on the face, the strange physiognomy, the poor emotional expression, hypomimicry, the immobile facies (l'air figé), the pseudodementia aspects and the salivation. The eyes show tremor of the lids, paresis of convergence and pupillary signs, which we shall describe later.

Though the general movements of the patient do not show any characteristics of such a preparkinsonian state, it is sometimes possible to surprise the patient in an attitude of slight flexion or in a catatonic posture, the pendulous movements of the arms when walking may be absent on one side or on both sides. The reflexes of posture (Foix and Thévenard) are increased in such a latent stage (Henner, 1925). In a detailed examination of the patient one finds several symptoms that reveal a disturbance of the extrapyramidal innervation (Signe de la roue dentée, Negro, the dissociation of forces, Mlle Dyleff, signe de l'arrêt brusque, Mlle Dyleff, signe du renversement du tronc en arrière, Souquea, signe du moulinet, Souques, and many others).

Fully Developed Encephalitic Parkinsonian Syndrome—The first case of parkinsonian syndrome was presented by one of us (L. S.⁸) at the meeting of the "Purkyně Society" in January, 1921. Since that time the parkinsonian syndrome has been noticed to be widespread. The symptomatology and pathophysiologic deductions of the encephalitic parkinsonian syndrome were discussed by one of us (L. S., 1922⁹).

8 Syllaba Čas lék čes., 1921, no. 10

9 Syllaba Čas lék čes. 61 1041, 1922

The symptomatology of the parkinsonian syndrome is so well known that it is not necessary to say much about the three primary symptoms

1 The loss of associated movements seems to be the first of the three primary symptoms

2 Rigidity is more apparent than real in some cases, the extrapyramidal qualities of the rigidity, especially its plasticity, are always present

3 Tremor is sometimes not conspicuous, it is often also intentional and present not only when at rest. There are forms "sine agitatione" and also "sine rigiditate". Some degree of loss of the associated movements is always present in both instances. The condition is never strictly symmetrical. Tremor and paresis of the tongue were present in every case without exception, it is also one of the earliest signs. Besides the three primary symptoms, many others have been observed which are somewhat familiar from the description of *paralysis agitans essentialis*

Disturbance of Speech—Some patients had Gowers' "festination in speech analogous to that in walking," i. e., Claude's tachyphemia. Such patients begin to speak in a normal way, but they speak more and more rapidly, until their speech becomes entirely incomprehensible. Palilalia (Souques) was also observed. Palilalia consists of involuntary and irresistible repetition of words or sentences (even thirteen times in our cases). Both types of patients were presented at our medical society (Henner, 1922¹⁰ and Scheiner, 1922¹¹). Several other cases of tachyphemia and palilalia were observed at our clinic, in these cases there was always marked retropulsion.

Difficulty in speech always occurred with the encephalitic parkinsonian syndrome and varied according to the tongue symptoms, which were always present. Usually speech was monotonous, but sometimes enunciation was also difficult. Such disturbances sometimes resembled bulbar or pseudobulbar speech (type II, Bissaud). Another striking factor was the low voice of the patients. Several patients could not speak at all—parkinsonian mutism.

Kinesia Paradoxa—This strange phenomenon occurred frequently. Almost every patient with the encephalitic parkinsonian syndrome could run better than walk, but the kinesia paradoxa occasionally was striking in almost all movements. The patient, for instance, could not say more than one or two words, extremely slowly and in a low voice, on some occasions, especially when angry, he spoke in a normal manner. The kinesia paradoxa was of short duration and most independent of the patient's will.

10 Henner Čas lek čes, 1922, no 19

11 Scheiner Čas lek čes 61 292 and 410, 1922

Later Evolution of Parkinsonian Syndrome—The parkinsonian syndrome is usually progressive, sometimes progress is rapid the wasting is excessive and death occurs in a short time usually as the result of an intercurrent disease (A progressive chronic stage, forme cachectisante, Mille Lévy)

Death occurred in eleven of seventy-two (15.3 per cent)⁶ of the cases which we observed at the clinic in the first months of 1920

The aggravation usually advances by leaps (schubweise poussée évolutive) After such an episode the condition of the patient again becomes stationary for some time We have not seen the spontaneous reappearance of the acute picture (lethargy delirium myoclonies etc) that some authors have noted

Other cases present a parkinsonian syndrome which does not change One could perhaps name such a condition 'status post encephalitidem ' We may imagine that in these cases the pathologic process is anatomically cured, and that there is no persistence of the virus in the nervous tissues

Differences Between the Encephalitic Parkinsonian Syndrome and Paralysis Agitans Essentialis—There are many cases in which the differential diagnosis would be entirely impossible if we did not know the history of the acute stage usually the encephalitic parkinsonian syndromes have various additional symptoms which are not common in Parkinson's disease It is especially the atypical intentional tremor the catatonic elements together with the pseudodemential physiognomy which are almost pathognomonic for chronic encephalitis

The Encephalitic Torsion Spasm (Dysbasia Lordotica Progressiva)—This form is rare, we observed it only in patients who had the acute stage as children Our clinic was the first to describe the 'parkinsonian syndrome of extension' and its close relationship to torsion spasm (Henner, 1922¹²) The parkinsonian syndrome of extension described by Charcot and Mendel is much more a torsion spasm 'fruste' than a shaking paralysis Our opinion is that the term parkinsonian syndrome of extension should not be employed The "parkinsonian syndrome of extension" has been observed at our clinic thus far in sixteen patients¹³ The extension is not so pronounced as the flexion in the frank parkinsonian syndrome of flexion, but the extension always became greater when the patient was standing or walking (dysbasia lordotica progressiva) A complete symptomatology of torsion spasm was seen in four cases One of them was described in detail and illustrated by moving pictures¹⁴ This patient had a well marked kinesia paradoxa, in playing with a ball, he was quick and skilful like a normal

12 Henner Čas lék čes 62:103, 1923

13 Henner Compt rend cong de med. alien et neurol, 1925, p 229

14 Henner Čas lék čes 63:797, 1924

boy Our cases of encephalitic torsion spasm showed clearly that the dysbasia lordotica progressiva is not a disease of only one etiology, but of one and the same topography of lesions (somewhere between the basal ganglions and the midbrain) Our four patients with complete encephalitic torsion spasm passed successively through these stages (1) acute encephalitis, (2) apparent recovery, (3) light frank parkinsonian syndrome, and (4) first signs of torsion spasm It is the only form of chronic encephalitis in which the parkinsonian syndrome is not the latest stage of the disease

Some Rare Additional Symptoms of the Chronic Stage—The Brady-Kinetic Movements (P Marie and Levy) As has been said, these movements were not seen at our clinic in the acute stage, in the chronic stage, we have seen them only three times (Henner, 1923) They are slow rhythmic movements of the limbs, the amplitude of the movements is great, and the localization is usually at the root of the limbs, some resemble tics, but the bradykinetic oscillations are too slow, and if one resists the movements, one may palpate the contractions of the muscles which persist as long as one holds the limb of the patient In all three cases, the bradykinetic movements were associated with a slight parkinsonian syndrome

Rhythmic clonic contractions were observed in six cases In one case¹⁵ they were in the whole region of the left seventh nerve These contractions occurred as often as thirty times in a minute, one contraction lasting from four to six tenths of a second (graphically registered) In this case also there was a slight parkinsonian syndrome The rhythmic contractions disappeared after the treatment by auto-cerebrospinal fluid Two years later, the patient had a marked parkinsonian syndrome, nevertheless he could play football as well as before he had the disease (kinesia paradoxa)

Median Facial Spasm (Meige) This picture following epidemic encephalitis apparently was not seen by any one else This phenomenon consists in a closing of the eyes for several moments, which is preceded by a progressive fascicular tetanization The patient makes various defensive movements in order to be able to stop the spasm Although at first it resembles a tic, it is not a tic, but an organic disturbance We had only one such case (Henner¹⁶) Tics may occur either after or during encephalitis One of us (L S¹⁷) presented two cases with well marked tics (in 1921), later, two others from our service were reported by Vondráček¹⁸ We divide encephalitic tics into early tics

15 Henner Čas lek čes 62 156, 1923

16 Henner Čas lek čes 62 102, 1923

17 Syllaba Čas lek čes 60 56, 1921

18 Vondráček Čas lek čes 61 410, 1922

which develop on the encephalitic basis and secondary later ties in which we presume the existence of general nervous degeneration. Many other types of tic were observed at our clinic later.

Myotonic Phenomena Myotonia is confined to a few muscles and is present especially in the hand grasp. The more firmly the patient grasps an object the more difficult it is to relax his hold. This phenomenon was observed only when the parkinsonian syndrome was present.

Mental changes were frequent and the variation in degree was great. Slight changes of character, inability to concentrate and suicidal tendencies were noted, but we have not seen a person with fully developed insanity who required seclusion. Of the three psychic elements—intelligence, emotion and will—the first is involved rarely in the adult; memory, observation and judgment were usually intact. A more or less pronounced egocentrism was not surprising in such a serious condition as chronic encephalitis. Many persons with chronic encephalitis are in a state of dementia (little expression on the face, open mouth and pyalism) but they are not demented. On the other hand the psychic life of such persons is sometimes poor and sometimes ended by the loss of contact with the exterior world when the somatic state does not allow the patient to read, write or speak. As a rule the real defect seems to be in the will, the majority of patients being hypobulic or abulic. Mental changes are much more serious in children, in whom we saw the most profound alterations; they became aggressive, showed pathologic tendencies, cruelty and a classical moral insanity; they often developed nocturnal restlessness and excitement. Drowsiness by day persisted in all patients a long time, especially in children.

Obesity, Polyuria, Diabetes Insipidus Several patients gained in weight in a pathologic manner; an increase of 10 Kg. in adults was not exceptional. Sometimes polyuria and thirst accompanied the obesity. One of our ambulatory patients drank 31 liters of water daily and had a corresponding polyuria. We could not perform the necessary tests to determine whether all characteristics of diabetes insipidus were present.

In one case a woman with an encephalitic parkinsonian syndrome gained 18 Kg. in one year. Her menses ceased and she had a slight polyuria (3 liters) and was always thirsty. That association of symptoms suggests *dystrophia adiposogenitalis*. That patient was presented by one of us (L. S.) to show that *dystrophia adiposogenitalis* may also be a syndrome caused by the topography of the lesions and that *dystrophia adiposogenitalis* is not always an independent disease. Such cases reveal the alteration of the floor of the third ventricle. Changes occur in the hypothalamic zone where the lesions of chronic encephalitis are relatively frequent. Thirst and secondary polyuria caused by

primary polydipsia may also be derived ultimately in some of these cases as a result of treatment with scopolamine

Sympathetic System One of us (L S), with Weber, examined the sympathetic system in the usual manner in from twenty-six to thirty-four cases of chronic encephalitis in which the parkinsonian syndrome was present¹⁹ The results of glycemie tests after 1 mg of epinephrine had been injected subcutaneously showed that only five of twenty-six patients had a normal reaction and twenty-one had an abnormal one The condition affects especially the mechanism of regulation, hyperglycemic reactions were too high, irregular and interrupted The glycemie curves after the ingestion of dextrose did not show any special abnormality, after the ingestion of levulose these curves were almost normal The blood pressure was usually lowered Weber thinks that this fact could be explained by alteration in the corpus striatum Vidal's test for hemoclasia was positive in only 20 per cent (seven of thirty-four) Rigidity did not change after the administration of epinephrine Tremor was constantly increased, especially after intravenous injection of epinephrine

To summarize We think that the alterations in the sympathetic system in chronic encephalitis are constant The lesions are probably situated particularly in the highest sympathetic centers

The liver seems to function normally in chronic epidemic encephalitis

Signs Common to all "Forms" and Pictures of Chronic Encephalitis—These signs have the greatest practical importance In its beginning a chronic stage of the disease often gives the impression of a functional trouble (neurasthenia or pithiasisme) When the symptoms are limited to one extremity, one thinks of a peripheral paresis

Pupillary Signs Every combination of loss and preservation of one or more of the five reactions may occur One of us (L S) was the first to describe the Argyll Robertson pupil in the acute and chronic stage of epidemic encephalitis The Argyll Robertson pupil was observed at our clinic also in the stage of latency during the interval of apparent recovery

The most frequent type in the chronic stage was the reverse Argyll Robertson pupil All reactions were preserved, and only the movement which normally results when looking closely was not present That type of pupillary symptom was not known before the occurrence of epidemic encephalitis, and it is almost pathognomic of that disease We have not seen that sign in any other disease

¹⁹ Weber Sborn lek, 1923, p 264 Svllaba and Weber Rev neurol, 1926, vol 1, no 6

Simultaneously with the disappearance of the reaction of accommodation we usually found paralysis or paresis of convergence of the eyes. The paresis of convergence is frequent too in essential paralysis agitans.

These oculopupillary signs were studied in the chronic stage of epidemic encephalitis by one of us (K. H.²⁰). Accommodation (the function of ciliary muscle) usually is not disturbed in the chronic stage.

Abnormal accommodation and paresis of convergence are usually associated, but we found that even these two functions may be dissociated in epidemic encephalitis.

The movement of the pupil which occurs on far or close vision is not a reaction to accommodation, it is not a true reaction, but an action which by physiologic conditions is associated with convergence of the eyes and changes in the refractivity of the eye lens. Chronic epidemic encephalitis has shown that each of these three functions may be attacked separately by pathologic conditions.

The disturbance in the accommodation reaction and paresis of eye convergence in our cases were greatest when the patient was looking up. They were sometimes less when he was looking forward and diminished still more when he was looking down (Bairé's rule). It is an exaggeration of normal physiologic conditions. We are accustomed to use near vision to look closely, especially when looking down, rarely when looking up. In that syndrome (paresis of convergence with loss of the accommodation reaction) the lateral movements of the eye-balls are normal.

Patients with Argyll Robertson pupils or with inactive pupils in the interval of apparent recovery would lead to error and should make one suspicious of neurosyphilis or metasyphilis. In a few cases that possibility should be seriously considered.

Other Ocular Signs of Chronic Epidemic Encephalitis. While in the acute stage we usually saw nuclear disturbances in the movements of the eyeball, in the chronic stage we saw chiefly disturbances of the movements of association. These were not paralytic, but irritative, they were not constant, but intermittent, and occurred in spasms. These spasms were characteristic. Both eyes were turned to the left or the right, but especially upward. In such an attack, the eyes were fixed, and they could not be moved in any direction. Such attacks occurred at certain intervals, usually at a certain time of the day, especially in the evening. In our cases, the deviation of the eyeballs was associated with different deviations or rotations of the head. These particular deviations of the eyes and head which appeared in spasms and while the patient was fully conscious were almost pathognomonic of chronic epidemic encephalitis. The cerebellar and vestibular functions were examined in

detail²¹ Almost all cerebellar examinations gave results which were just the opposite of those obtained in cases in which destructive cerebellar lesions were present This reverse condition was brought out when one compared a case of encephalitic parkinsonian syndrome with a case of definite cerebellar lesion (eating, walking, dressing etc) In 1925, we²² showed that what in a destructive cerebellar syndrome was "black" in a parkinsonian syndrome was "white" and vice versa Some parkinsonian symptoms were present in almost every case of cerebellar lesion, that is, in some cases examinations did not show that the patients were normal or that they had cerebellar lesions, but the results were the opposite of those obtained when cerebellar lesions were present We are inclined to consider such results as irritative or hyperfunctional cerebellar signs That point of view found support in the results of our experimental investigation When alcohol is given to a normal person, it creates an excessive cerebellar deficiency syndrome (classical) accompanied by exaggerated (and partly impaired) responses on instrumental vestibular irritation We found an analogous effect after big doses of scopolamine (from 1.2 to 1.6 mg in from five to ten hours)

A patient with a cerebellar lesion which was already much compensated and whose cerebellar symptoms disappeared again presented a full deficiency cerebellar syndrome after a small dose of an alcoholic drink or after taking a few decimilligrams of scopolamine

On the contrary, patients with the encephalitic parkinsonian syndrome were much improved temporarily by one or the other drug Almost all symptoms disappeared or were diminished considerably in accordance with the diminution of postural reflexes (Forx and Thevenard) By increasing the dose of the drug, we could even change some parkinsonian symptoms into cerebellar (deficiency) signs

Vestibular examination in patients with the encephalitic parkinsonian syndrome did not show any special changes in the nystagmus produced but the reactive movements were much less than in a normal person These reactive movements became greater during intoxication from alcohol or scopolamine In the past-pointing test of Barany and in the examination of Hautant a regular tendency to a spontaneous inside deviation was found (In destructive cerebellar lesions a spontaneous outside deviation almost always occurs) Apparently the parkinsonian syndrome has the aspect of a general cerebellar hyperfunction

In the monograph mentioned (Henner), we said that we are conscious of many possible objections, nevertheless, the finding of a conse-

21 Henner Symptoms Caused by Hyperfunction of the Cerebellum, Sborník 1924, p 1

22 Henner Rev. neurol 1 1048, 1923

quent antithetic parkinsonian cerebellar syndrome is too regular and constant. One can hardly interpret everything as a mere chance.

There is a great variation in the association of the symptoms in all the chronic "forms" of chronic epidemic encephalitis, and it is not possible to speak about many well marked "forms." We recognize only the following somewhat distinctive symptoms:

- 1 Parkinsonian syndrome

- 2 Torsion spasm (its incomplete clinical picture is the "parkinsonian syndrome of extension")

- 3 The infantile form which is characterized by profound mental changes, prolonged inverted type of sleeping, however, the infantile form is or becomes in the end parkinsonian

- 4 Dystrophia adiposogenitalis (in women), obesity in men, diabetes insipidus even with the association of the parkinsonian syndrome was constant

The prevalence of extrapyramidal manifestations was extremely striking in the chronic stage.

We are not trying to develop any conceptions of the logic pathologic physiologic processes of the chronic stage of epidemic encephalitis from what this disease taught us about the normal functions of several systems in the human brain. Our intention is only to communicate the clinical conditions which we have observed and studied.

DIAGNOSIS AND PROGNOSIS

In the acute stage of the condition one must in doubtful cases consider especially tumor of the brain, meningitis, the catatonic form of dementia praecox and syphilis of the brain stem. The differentiation is usually easy, especially after a thorough examination of the cranial nerves and the cerebrospinal fluid, nevertheless in some cases the diagnosis may be difficult.

In the chronic stage, the diagnosis is still easier to make. An authentic paralysis agitans and especially syphilis of the brain must be considered. Following an epidemic of encephalitis, one must consider not only syphilis and metasyphilis, but also epidemic encephalitis in every case of pupillary disorder.

Syphilis of the brain and epidemic encephalitis may sometimes have the same clinical picture. There are also syphilitic parkinsonian syndromes and syphilitic encephalitis of the corpus striatum which have been described and histologically proved (Lhermitte, Roussy and Cornil).

It should not be forgotten that a syphilitic person may become affected by epidemic encephalitis as well. We have described several

cases in which it was practically impossible to decide whether the condition was syphilis or chronic epidemic encephalitis (Henner)

The Wassermann reaction was sometimes positive in epidemic encephalitis even when syphilis could be excluded. The unreliability of the Wassermann reaction in every infectious disease is now well known. In such cases careful examination of pupils, especially of the inverted Argyll Robertson type, the paresis of convergence is helpful.

This seems to be difficult. If the acute symptoms are not too violent, if the fever is not high, if the sensorium is not much disturbed, it is easy to say that the patient will live for several months or years. Even after our extensive experience we cannot predict in any given case that the patient will recover completely even though he may appear well following the acute stage of the condition and even though he has been well for several years (L. S.). There are also no signs that could tell us whether a chronic stage is stationary, whether it is a sequel, a status postencephaliticus, or whether it is or will become a progressive evolutionary form.

TREATMENT

In accordance with Levaditi's experience, we used for prophylaxis potassium permanganate (2:1,000) for disinfection of the mouth and nasopharynx. We did not have any case of infection either among the medical staff or among the other patients, nevertheless, it is almost certain that the same results could be obtained without that precaution.

Treatment in the Acute Stage—We began to use Levaditi's virus vaccine intrathecally in 1925. Three patients were treated (Henner²³), and they apparently recovered completely, nevertheless, it is difficult to say that the same result would not have been obtained without the virus vaccine, and that recovery will be permanent and will not be followed by a chronic stage.

Other Treatment—In 1920, we gave our patients only methenamine, and the results during that year were the least favorable obtained. But the clinical picture at this time was also the most serious during the six years. Since 1920, following the adoption of more energetic treatment none of our patients has died in the acute stage of the disease, but one cannot say that the same results could not have been obtained without treatment.

Lumbar puncture seems to be useful in the acute stages. We always used an intrathecal injection of methenamine and an injection of the autocerebrospinal fluid subcutaneously. That treatment was repeated several times, once a week, during the acute stage. In the intervals, we gave daily 1 Gm. of 25 per cent methenamine solution intravenously.

The great excitation, especially in the myoclonic form, was markedly benefited by the intramuscular injections of bromhydrate of conine from 1 to 2 mg

Several cases were so serious that we expected the patients to die, nevertheless, they recovered. Our opinion, therefore, is that treatment probably has an influence

During the period of apparent recovery our patients were advised to lead a hygienic life such as is recommended in any nervous disease, and they received methenamine periodically either by mouth or intravenously

Treatment in the Chronic Stage—Many patients²⁴ had been treated by the virus vaccine of Levaditi. One patient developed bronchopneumonia during the treatment and died, having received the vaccine by the suboccipital route. With the exception of this patient, none of the others grew worse following treatment, the majority did not get the full dose, the vaccine was not always fresh, and the intervals were sometimes too long. It is therefore difficult for us to appreciate the real value of the virus vaccine. Several patients who had the parkinsonian syndrome, especially children, improved considerably on that treatment.

By the use of the vaccine we could shorten the duration of the chronic form of the disease by several days and change it into an acute, typical and classical oculolethargic form. This result could not be produced by any other means, but it must be remembered that we have not had any experience with intrathecal injections of other protein bodies.

The reactions were violent. The lethargy was often like that in an acute stage of the disease, and was followed by delirium during the night. The inverted type of sleeping would occur for a time, the meningeal phenomena were usually more marked during the first days of the reaction than in a spontaneous acute epidemic encephalitis. The reaction usually had two apexes of fever which were separated by an interval of normal temperature. Is it that the first fever is "para-specific," and the second, "specific?"

The vaccine seems to be specific, and that is the most hopeful factor. One cannot ask more even from a specific vaccine when used in the chronic stage than that it will stop the inflammatory part of the process and give the patient a persistent immunity. The purpose is to change a chronic encephalitis to a postencephalitic state, to change an evolutionary form into a stationary form. The later treatment of a patient anatomically cured by the vaccine resolves itself into physical measures.

All these facts show how impossible it is as yet to say anything definite about the value of the virus vaccine.

We also used a cacodylate of sodium (50 per cent solution) in a large series of cases. We used it intravenously in large doses (K H^{25}), from 0.5 to 2.5 Gm., given three times a week in several series of cases. Several hundred patients were treated in that manner. Almost every patient improved after this routine (from about 40 to 70 Gm., intravenously), but the ultimate results were striking in only a few cases. The best results occurred in cases in which the Wassermann reaction was positive. It may be that these cases were associated with syphilis of the brain and that the cacodylate of sodium had the antisyphilitic action attributed to this remedy by American authors. We have about twenty patients who were not able to do any work and who are now able to carry on their occupation in a satisfactory manner. Nevertheless, typical objective pathologic signs were not absent in any case after treatment.

Scopolamine and scopolia taken by mouth or injected subcutaneously had the quickest, the most marked, but also the most temporary effect, nevertheless the getting accustomed to it was slow and there are many patients who have lived for several years on scopolamine and whose life that remedy has made relatively supportable. Many other treatments were investigated.

Intravenous injections of autocerebrospinal fluid (Henner and Baroch, 1924²⁵) were without notable effect. Only the patient with rhythmic clonus whom we have already mentioned lost the clonic jerks after that treatment but not the signs of a slight parkinsonian syndrome.

The intravenous injections of sodium salicylate and intrathecal injections of autoserum have not been tested in a sufficiently large series for us to offer a definite opinion concerning their efficacy.

PHYSICAL REEDUCATION

Active and passive movements, massage and prolonged baths may have a good influence in every case when everything is done systematically and with great perseverance and energy.

We are neither nihilists nor absolute skeptics concerning the treatment of patients who have chronic epidemic encephalitis, but this disease has shown us that definite statements about the value of this or that therapeutic method cannot be given until after many years have elapsed.

CONCLUSIONS

Epidemic encephalitis as observed and studied at our clinic from 1920 to 1924 was and is to us a new disease. Our opinion is that it is a distinct and independent disease, and, for many reasons, we do not believe that we are justified in naming or confusing it with influenza.

Epidemic encephalitis is a complete clinical pathologic and anatomic entity

Mortality in the acute stage was not high in our series, but the chronic stage caused great devastation

The treatment should be prompt and energetic in the acute stage in which recovery is more or less dependent on medical care. Treatment in the chronic stage is not *a priori* absolutely hopeless, but it is tedious and the results are uncertain

Several years of the pandemic of epidemic encephalitis have influenced the whole neurologic world in an unexpected way. We have gained more knowledge of the physiology and pathology of the extrapyramidal system during this pandemic than we should otherwise have done in several decades. The extrapyramidal symptomatology from now on is based on a secure neurologic basis and forms a new neurologic chapter

Nevertheless many questions concerning epidemic encephalitis remain unanswered. The most important questions seem to be the solving of the actual problem during such a rare outbreak of epidemic encephalitis (once or twice in a century), determination of the cause of the long period of apparently complete recovery which often occurs between the acute and the chronic stage, the reason for the prevalence of extrapyramidal signs in the chronic stage, the treatment in the chronic stage.

Our article does not deal with a new theme, nor is it a clinical description of epidemic encephalitis. Omitting almost everything that is general knowledge we have intended simply to present our personal observations and opinions which we have gathered from the thousand cases of encephalitis that we studied.

ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS

THE ABSORPTION OF UNALTERED FISH PROTEINS IN ADULTS *

MATTHEW BRUNNER, M D

AND

MATTHEW WALZER, M D

NEW YORK

In a previous communication, one of us¹ presented a direct method for demonstrating the absorption of undigested protein in human beings. The technic employed was described in detail. The following routine was adopted for studying the absorption of unaltered fish protein.

The subject to be studied was kept on a fish-free diet for twenty-four hours and was then passively and locally sensitized to fish by the intradermal injection on the arm of 0.05 cc. of a suitable serum. This had been obtained from two patients sensitive to fish, "G" and "M," whose histories were presented. On the following morning, the subject was fed about 50 Gm., or one third, of a raw herring, on an empty stomach. Within from a few minutes to two hours, a reaction consisting of pruritus, erythema and a wheal usually developed at the sensitized site. It was proved that this reaction could only be effected by the union of the reagins, in the serum obtained from persons sensitive to fish, which had been fixed at the injected site, with the specifically related protein, unaltered fish protein. Its appearance after ingestion of fish, therefore, was a specific indication that unaltered fish protein had penetrated into the circulation from the digestive tract. The details of serum preparation, the technic for passive local sensitization and for testing and a theoretical discussion of the various principles involved in the procedure have all been presented in the first communication. A detailed description of the local reaction has also been presented elsewhere.²

The scope of the present communication is limited to the results of studies on the absorption of unaltered fish protein in adults, with a notation of a few of the factors which were found to affect the phenomenon.

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1 Walzer, M. J. Immunol. **14** 143, 1927.

2 Walzer, A., and Walzer, Matthew. Am. J. M. Sc. **173** 279, 1927.
Urticaria. II Arch. Dermat. & Syph. **17** 659 (May) 1928.

PRELIMINARY STUDIES

In order to ascertain the usual reaction (absorption) time in the average person and to determine the dilution of serum most favorable for testing purposes, a number of subjects were chosen who, as far as could be determined, were free of gastro-intestinal disturbances. The first twelve cases recorded in table 1 comprised this group. The usual routine was employed, except that each subject was sensitized with two or more dilutions of serum, as noted in the table. The reaction (absorption) time was measured from the time of the ingestion of fish to the first objective symptom noted at the sensitized site, namely, erythema or a wheal. Pruritus, though it often was the first to appear, could not be accepted as a reliable index of the onset of the reaction as it was a subjective symptom, which could not be confirmed by the investigator. The results of the tests appear in table 1.

In charting results, it was found difficult to record the degree of the reaction, except in a general manner. It was noted, however, that within broad limits and with a few exceptions the stronger the reaction the earlier its appearance, and vice versa. As the reaction time was a definitely measurable quantity, it was therefore chosen, in preference to the size of the reaction, as an index of the subject's absorptive powers.

In the preliminary series, each of the six subjects sensitized with undiluted serum demonstrated the phenomenon. Of twelve subjects sensitized with a 1:10 dilution, eleven reacted positively. Of eight tested with a 1:100 dilution, only three reacted, with a 1:200 dilution, only one positive result was obtained in four subjects tested. Case 8 was the only instance in which positive reactions were not obtained. Unfortunately, this subject had not been tested with undiluted serum and was unable to return for further investigation.

These preliminary tests demonstrated that dilution of the serum in excess of 1:10 materially diminished its usefulness. Up to that point, however, dilutions were almost as effective as the whole serum. For the purpose of economy and, at the same time, to avoid the severe local reactions which often occurred with the undiluted serum, the 1:10 dilution was adopted for routine sensitization. When this gave negative results, the test was repeated when possible, the undiluted serum being used.

With the exception of case 4, which will be discussed presently, the reaction time in persons sensitized with the 1:10 dilution varied from five to sixteen minutes, and with the undiluted serum, from six to thirteen minutes.

RESULTS OF TESTS

With the foregoing information as a guide, a series of studies were instituted on a variety of subjects. In all, sixty-five subjects were tested. Their ages varied from 15 to 70 years. About three fourths of

TABLE 1—Results of Tests

Case	Date	Diagnosis	Age	Sex	Sensitizing Serum	Reaction (Absorption) Time in Minutes			
						Undiluted Serum	Dilution 1 10	Dilution 1 100	Dilution 1 200
1	9/20/25	Normal	31	M	G	9	9		
2	9/20/25	Normal	28	M	G	13	13	+	0
3	9/20/25	Normal	32	M	G	6	5	24	
4	9/20/25	Normal †	31	M	G	26	60	0	
5	9/20/25	Normal	36	M	G	9	9		
6	9/20/25	Normal	23	M	G		16	0	0
7	9/20/25	Normal	25	M	G		10	0	
8	9/20/25	Normal	31	M	G		0	0	
9	9/20/25	Normal	25	M	G		5	1	
10	9/20/25	Normal	33	M	G		15	0	0
11	9/20/25	Normal	30	M	G		10		10
12	9/20/25	Normal	30	M	G	13	13		
13	9/20/25	Asthma	34	M	G	15	0		0
14	9/20/25	Asthma and hay-fever †	27	M	G	40	0	0	
15	9/20/25	Asthma and hay-fever	33	M	G	9	9		
16	9/23/25	Bell's palsy, hypertension	41	M	G		+	25	
17	9/23/25	Cerebrospinal syphilis	39	M	G		23	28	
18	9/23/25	Infectious arthritis	37	M	G		26	47	
19	9/23/25	Asthma	50	M	G		5	5	
20	9/23/25	Miliary tuberculosis	27	M	G		0	0	
21	9/23/25	Typhoid fever convalescent	17	F	G		11	17	
22	9/23/25	Carcinoma of breast	36	F	G		18	31	
23	9/23/25	Pneumonia and pleurisy	50	F	G		8	8	
24	9/23/25	Pneumonia	32	M	G		60	60	
25	9/26/25	Purpura	23	F	G		14		
26	9/26/25	Shoulder injury	23	M	G		19		
27	9/26/25	Osteomyelitis	16	M	G		29		
28	9/26/25	Hernia	70	M	G		17		
29	9/26/25	Hysteria	28	F	G		2		
30	9/26/25	Cholecystitis	40	M	G		20		
31	10/14/25	Gastric ulcer	41	M	G		27		
32	10/14/25	Asthma	50	M	G		15		
33	10/16/25	Scleroderma	Adult	F	G		14		
34	10/16/25	Pemphigus	Adult	M	G		29		
35	10/16/25	Raynaud's disease	Adult	F	G		32		
36	10/16/25	Pemphigus	Adult	M	G		13		
37	10/16/25	Pemphigus	Adult	F	G		18		
38	10/16/25	Ikeloid	Adult	F	G		26		
39	10/18/25	See table 3	52	M	G	60	0		
40	10/18/25	See table 3	40	M	G		75		
41	10/18/25	See table 3	37	M	G	105	0		
42	11/20/25	Normal	Adult	M	G		12		
43	11/20/25	Normal	Adult	M	G		5		
44	11/20/25	Normal	Adult	M	G		5		
45	12/19/25	Pneumonia	32	F	G		15		
46	12/19/25	Normal	48	F	G		7		
47	12/19/25	Normal	23	F	G		16		
48	1/20/26	Urticaria	27	M	G		9		
49	4/17/26	Hookworm	37	M	M ₂	0	0		
50	5/ 9/26	Asthma	16	F	M ₂		32		
51	5/ 9/26	Asthma	38	M	M ₂	40			
52	5/ 9/26	Asthma	18	F	M ₂	27			
53	5/ 9/26	Asthma	50	M	M ₂	0	0		
54	5/12/26	Asthma	35	F	M ₂	60	0		
55	5/15/26	Angioneurotic edema	21	F	M ₂	25	20		
56	5/15/26	Angioneurotic edema	20	F	M ₂	50	0		
57	6/16/26	Asthma	50	M	M ₂	8	16		
58	6/ 5/26	Normal	43	M	M ₂	10			
59	6/ 5/26	Normal	42	F	M ₂	7			
60	1/15/27	Asthma	48	M	M ₃	15	15		
61	1/15/27	Asthma	15	M	M ₃	60	0		
62	1/15/27	Asthma	31	M	M ₃	15	25		
63	1/15/27	Asthma	52	M	M ₃	13	15		
64	1/15/27	Asthma	42	M	M ₃	22	55		
65	1/15/27	Asthma	55	M	M ₃	48	0		

* A positive reaction, the exact time of which was not noted

† See table 3

the series were males. Some of the subjects were patients in hospitals, convalescing from illnesses or minor operations. Others were chosen from allergic and dermatologic clinics. With the exception of an occasional case of gastric or duodenal ulcer or cholecystitis, most of the patients were free from serious gastro-intestinal disturbances. Many supposedly normal persons, free from any obvious illnesses, were included in the series as controls. It will be noted, however, that many of these so-called normal persons had unusual absorption times, while many patients in whom there was definite evidence of gastro-intestinal disturbances responded normally.

Some of the important observations which may be gleaned from an analysis of table 1 are given in table 2.

Of the four patients who failed to react, two were not tested with undiluted serum, as, unfortunately, they were unable to return for further

TABLE 2—*Analysis of Table 1*

	Serum Dilution			
	Undiluted	1 10	1 100	1 200
Number of cases tested	27	61	18	5
Number of cases demonstrating absorption phenomenon	25	49	11	1
Percentage of cases demonstrating absorption phenomenon	92.6	80.3	61.1	20
Total number of cases in series				65
Total number of cases failing to manifest the phenomenon in all dilutions tested				4
Percentage of cases demonstrating the absorption phenomenon				93.8

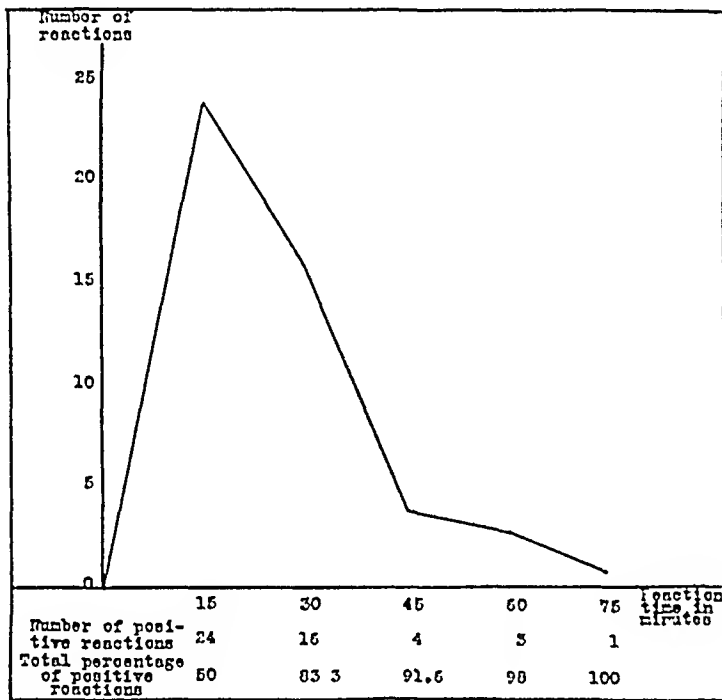
study (cases 8 and 20). Had they been so tested, it is possible that the percentage of failures in this series would have been even less than 6.2. Three of these four patients were tested intradermally at the site of injection with fish extracts, to determine whether they had accepted passive local sensitization. Positive reactions were obtained in all, thus definitely indicating that failure to demonstrate the phenomenon in these cases was not due to lack of sensitivity of the site of injection. This did not leave any other alternative but to accept the negative reaction as indicative of the fact that unaltered fish protein was not being absorbed from the enteric tract in these persons.

REACTION (ABSORPTION) TIME

It was found that in 50 per cent of the patients reacting with the 1:10 dilution, the reaction started within the first fifteen minutes after the fish had been eaten, and in 83.3 per cent, within the first half hour, as shown in the accompanying illustration. Any reaction time in excess of thirty minutes was therefore considered tardy and abnormal. The shortest reaction time was two minutes (case 29). This was a patient

with hysteria in whom a gastric extraction showed diminished secretion of hydrochloric acid. The longest reaction time in this series was 105 minutes, occurring in case 41, which will be discussed under another heading.

The reaction times with the undiluted serum and with the 1:100 and 1:200 dilutions are all tabulated in table 1. Though only a few of each were done, sufficient data were obtained to demonstrate that sites sensitized with concentrated serum usually responded sooner than those in which dilutions were used. Some exceptions to this rule will be discussed presently.



Graph representing reaction (absorption) times in the forty-eight patients sensitized with a 1:10 dilution of serum who demonstrated the absorption of unaltered fish protein.

FACTORS AFFECTING THE REACTION TIME

When early in the studies the patients in cases 4 and 14, who were brothers, were found to have delayed reaction times, other members of the family were similarly tested. As recorded in table 3, subject 39, the father of these two patients and his two brothers, cases 40 and 41, all were found to have a definitely retarded absorption time. A definite tendency to disorders which characterize the so-called allergic or atopic persons, including hyperacidity, asthma, hay-fever, vasomotor instability, etc., and a constant eosinophilia, were found in the members of this family group (table 3).

In order to determine whether the delayed reaction time was characteristic of all atopic persons, a series of patients with hay-fever and asthma were tested. The patients in cases 13, 14, 15, 19, 32, 50, 51, 52, 53, 54 and 57 (table 1) were tested with G and M₂ serum. Of these eleven patients eight reacted tardily or not at all. Of six tested with M₃ serum, cases 60 to 65, inclusive (table 1), four manifested delayed or negative reactions. Of three patients with urticaria or angioneurotic edema (cases 48, 55 and 56), which are considered by most authorities as atopic disorders, one showed a delayed reaction time. Therefore of this entire group of twenty subjects with atopic disorders, thirteen, or 65 per cent, manifested delayed reaction times. Hence, it may be concluded that, as a class, the atopic persons do not demonstrate

TABLE 3—*A Familial Tendency to Diminished Absorption of Unaltered Protein*

Case	Familial Relationship of Subjects	Age	Clinical Symptoms	Eosinophilia	Reaction Time in Minutes for Unaltered Fish Absorption	
					Undiluted Serum	Dilution 1:10
39		52	Recurrent vasomotor rhinitis	10 to 12% (3 counts in 2 years)	60	0
4	Son of patient in case 39	31	Hyperacidity, recurrent bronchitis with wheezing respiration, vasomotor instability	5 to 8% (3 counts in 3 months)	26	60
14	Son of patient in case 39	27	Hay-fever and asthma	5 to 6% (3 counts in 3 months)	40	0
40	Brother of patient in case 39	40	Hyperacidity, recurrent bronchitis with wheezing respirations	5 to 6% (3 counts in 3 months)		75
41	Brother of patient in case 39	37	Hyperacidity, recurrent bronchitis	0 to 4% (3 counts in 3 months)	105	0

the phenomenon of unaltered protein absorption to the same degree and with the same frequency as do nonatopic persons.

As already noted in the preceding communication, the performance of the test on a nonfasting stomach served to prolong the absorption time or to prevent the phenomenon entirely. This was best illustrated in the case of subject 16 who, on the morning of the test, ate his usual breakfast of oatmeal, one egg, two slices of bread and two glasses of milk. Following the ingestion of the fish two hours later, the local reaction at the sensitized site failed to appear. On the following day, breakfast was omitted and the herring eaten on a fasting stomach. This time a marked reaction developed at the sensitized site in about twenty minutes. In other cases, the administration of food preceding or with the fish did not entirely prevent the reaction but only delayed its appearance and diminished its intensity.

In a few of the patients with delayed absorption time, the administration of 1 or 2 drachms (3.9 or 7.8 Gm.) of sodium bicarbonate in an ounce (30 cc.) of water immediately preceding the ingestion of fish materially hastened the onset of the reaction. In case 32, in which the reaction time on three different tests was forty-five minutes or longer, the administration of sodium bicarbonate brought on the reaction in thirteen and fourteen minutes, respectively, on the two occasions when it was employed. Similar results were noted in other cases and in the studies on egg absorption.

The reaction time may be affected by altering the nature of the fish. Baking, cooking, pickling, soaking, canning or smoking the herring delayed or prevented the reaction.

Of less importance as a factor in the rapidity of the reaction is the site of passive local sensitization. As already noted in the previous communication, reactions on the forearm may be as much as ten minutes later in starting and are usually less marked than those in similar sites on the arm. The sites on the thigh and arm are usually alike in their reactivity. The reaction on the hand, in this respect, is similar to that on the forearm. The tardiness in the reactivity of the sites on the forearm is probably responsible for some of the unusual results noted in the earlier studies. For, as in cases 3 and 9, the reaction time with the diluted serum was shorter than with a more concentrated one, which was contrary to the usual rule. In the preliminary studies, however the arm and forearm were employed indiscriminately for local sensitization, hence the discrepancy.

THE SIGNIFICANCE OF NEGATIVE REACTIONS

The patient in case 49, who had hookworm disease, was one of the few who did not manifest the reaction at any time, even with the undiluted serum. He was subjected to considerable investigation in an effort to determine the cause of this refractoriness. Failure to accept passive local sensitization was ruled out as a cause by direct intradermal testing of the injected site with a fish extract, a marked positive reaction resulted. To insure against the possibility that in this person the fish was being retained in the stomach for an unusually long time, a duodenal tube was passed and allowed to remain in situ till, after eighteen hours, fluoroscopic examination showed the bulb well past the pylorus. Through this tube, herring which had been finely ground was injected. Again a reaction did not appear. Introduction of a similar preparation of herring into the rectum also gave negative results. The administration of sodium bicarbonate preceding the ingestion of the fish did not alter the result.

In order to determine whether this condition of impermeability existed for other proteins as well, all of the foregoing investigations were

repeated on the same subject with egg, with the use of the K egg serum. The same negative results were obtained as with the fish.

The conclusion, therefore, could not be avoided that, in this case at least, the failure of the reaction to appear indicated a real impermeability of the entire gastro-intestinal tract to the protein in its unaltered state. However, a negative result is not always to be interpreted in this manner, as there are other factors involved, some of which have already been discussed in this and previous communications, which may interfere with the reaction.

SUMMARY

1 The absorption of detectable amounts of unaltered fish protein from the digestive tract is a normal phenomenon, as it occurred in 93.8 per cent of sixty-five persons tested.

2 In 50 per cent of the subjects, the presence of the unaltered fish protein was detected in the blood stream within fifteen minutes and in 83.3 per cent, within one-half hour after its ingestion.

3 Atopic patients and some atopic families show a tendency toward diminished or negative reactions.

4 Some additional factors which were found to affect the reaction time are (a) contents of the stomach, (b) administration of alkalis preceding the fish meal, (c) the nature of the fish ingested and (d) the site of passive sensitization.

5 In a patient with hookworm disease, the negative reaction was demonstrated to be due to a true lack of permeability to egg and fish throughout the entire alimentary tract, including the rectum.

ALPHA LOBELIN AS A RESPIRATORY STIMULANT

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Alpha lobelin is an alkaloid which was first isolated from *Lobelia inflata* by Heinrich Wieland,¹ and shortly afterward studied pharmacologically by his brother, Herman Wieland.² This alkaloid in pure forms was supposed to be without the toxic effects shown by the older preparations of lobelia, and at the same time to have a marked stimulatory effect on the respiratory center. Herman Wieland claimed that it had specific stimulating action on that center, but that large doses would not produce vomiting, that vagus depression was absent, that there was no cumulative action, and that no lethal dose could be developed, even with the use of one hundred times the physiologic dose. It was also supposed to be a physiologic antidote to respiratory poisons such as morphine, chloral hydrate and carbon monoxide. The alkaloid was first tested clinically by Eckstein, Rominger and Wieland,³ who reported it of value as a respiratory stimulant. More recently, however, the drug has been studied by various American authors, and their results differ considerably from the foregoing observations. Norris and Weiss,⁴ after considerable work both on human beings and on animals, concluded that the action of the drug was variable, that its stimulation of the respiratory center was inconsistent, and that at times it was actually dangerous. They showed, furthermore, that repeated doses resulted in depression of the respiration instead of stimulation, and that there was a consistent fall in the blood pressure, averaging about 50 mm of mercury. Camp⁵ claims that it is not a specific stimulant of the respiratory center and that the other effects can be ascribed to the nicotine-like action on the

* From the McGill University Clinic, Royal Victoria Hospital, Montreal.

1 Wieland, Heinrich. Ueber die Alkaloide der Lobeliaphalanzen. Berl d Deutsch Chem Ges, 1921, liv, 1784.

2 Wieland, Herman, and Mayer, R. Pharmakologische Untersuchungen am Atemzentrum. Die Beeinflussung des markotisierten oder morphinisierten Atemzentrums durch Lobelin und zwei weitere Lobelin Alkaloide. Beobachtungen ueber die Kreistaufwirkung des Lobelins, Arch f exper Path u Pharmacol, **92** 195, 1922.

3 Eckstein, A, Rominger, E, and Wieland, H. Ztschr f Kindersheit **28** 218, 1921.

4 Norris, V H, and Weiss, S. The Pharmacological and Therapeutic Properties of Alpha Lobelin, J Pharm & Exper Therap **31** 43 1927.

5 Camp, W J R. Alpha Lobelin. A Pharmacological Study, J Pharm & Exper Therap **31** 393, 1927.

ganglions of the autonomic nervous system. He also advises caution in its use and warns against intravenous administration.

The present investigation was undertaken to test especially the action of alpha lobelin on the respiratory center both under normal conditions and when that center was depressed by various drugs. Observations were made also to decide whether any ill effects were associated with its use.

TECHNIC

The ampules of alpha lobelin as supplied by E. Bischoff were used in these experiments, the ampules having been shown by others⁴ to have the same physiologic action as the crystalline forms of the drug. As a basis for consistency in dosage 10 mg of the alkaloid was injected subcutaneously into a person weighing 150 pounds (68 Kg). Other doses were used, but this one was taken as normal for comparative observations.

The depth and rate of respirations were recorded by a pneumograph and controlled by an automatic timing device. The ventilation was measured by collecting all the expired air in a series of Douglas bags, and in this manner it was possible to ascertain accurately the gaseous exchange not only for a considerable period of time, but an average for each individual respiration. The expired air thus obtained was analyzed on the Henderson modification of the Haldane apparatus. In some human beings and dogs, arterial blood was collected both before and for varying periods after the administration of lobelin. The carbon dioxide content of this blood was measured, showing the carbon dioxide tension to which the respiratory center was reacting.

All tests of the drug were made while the person or the dog was at complete rest and without food for at least fourteen hours so that the estimation would not be affected by any metabolic factors. Depression of the respiratory center was produced by doses of morphine or chloral hydrate sufficiently large to cause an appreciable depression. One person with uremia in whom the respiratory rate had fallen to six per minute was also examined, but the results were disappointing, as will be detailed later. In the entire series, thirty-one experiments were made on ten different persons and on two dogs. The men were convalescent from various illnesses, some had cerebrospinal syphilis, but in all the respiratory mechanism was functioning normally.

PNEUMOGRAPHIC RECORDS

Much information can be obtained from pneumographic tracings, but where the variations are slight as was the case at times in this series, it is unreliable save as to the respiratory rate. It is almost impossible to judge accurately the depth of the respiratory movements in this manner because of the slight variations in successive respirations. A better index of respiratory efficiency is to be found in the measurement of the total ventilation as indicated by the collection, measurement and analysis of the expired air. Any change in the respiratory rhythm, such as the appearance of Cheyne-Stokes breathing, however, can be shown only by pneumographic tracings and it is for recording rhythm and rate that these tracings were made. After the administration of alpha lobelin

there was to be found slight, if any, variation in the tracing indicative of respiratory stimulation, while in practically every case stimulation actually took place, as shown by the gaseous exchange

Chart 1 shows this very well. In this instance the pneumographic tracing shows a doubtful increase in excursion, while there was an actual increase of 28.2 per cent in the average volume of each respiration for the five minute period following the administration of lobelin. In several instances there was an appreciable change in rhythm, twice the development of typical Cheyne-Stokes type of respiration and again the presence of apnea.

Chart 2 shows a respiratory rhythm approaching the Cheyne-Stokes type which appeared fifteen minutes after the administration of lobelin. Apnea followed once about thirty seconds after the intramuscular administration of 10 mg. of lobelin and was accompanied by cyanosis, marked slowing of the pulse rate, coldness of the extremities and profuse perspiration. After about forty-five seconds the respiratory movements began to return slowly, but the patient vomited repeatedly and was unable to eat for the remainder of the day. The sudden toxic effect can be explained by the possibility that the drug may have been introduced into a vein and caused temporary paralysis of the respiratory center with stimulation of other medullary centers.

TOTAL VENTILATION AND RESPIRATORY VOLUME

In all but two instances there was a decided increase in the ventilation per minute following the use of lobelin varying from 12.81 to 68.3 per cent, with an average of 31.25. This statement is based on observation of persons exhibiting normal respiratory mechanisms that are not depressed by drugs. Following respiratory depressants, however, the results are somewhat different as will be detailed later.

In deciding whether or not a drug is a respiratory stimulant, it is necessary to find that an increase in ventilation per minute has taken place, but this in itself is not a sufficient criterion, because it might have been produced merely by an increase in rate. If this were the case, stimulation would be more apparent than real. There might, in fact, be a depression because of the decreased opportunity for the exchange of gases in the lungs. Stimulation presumably occurs with little or no increase in rate, but rather with an increase in the depth of each respiration. Under these circumstances, there is not only an increase in total ventilation, but a better opportunity for gaseous exchange. These requirements the use of alpha lobelin meets, for there followed its administration not only an increase in total ventilation per minute, but a decided increase in the volume of each respiration, varying from 1.02 to 50.70 per cent with an average of 14.98 per cent. Following the administration of lobelin there is, then, not only an apparent but also a real,

stimulation of the respiratory mechanism. It was most marked about fifteen minutes after injection, and after that time the effect gradually decreased until at the end of thirty minutes conditions were similar to those before the drug was given. Two cases in the series, however, while showing a striking increase in ventilation per minute, exhibited an actual decrease in the volume of each respiration. These decreases amounted to 15.7 and 27.35 per cent, respectively, and are to be explained by the marked increase in the respiratory rate. It is doubtful, therefore, whether in these instances there was any beneficial effect on the respiratory efficiency.

ANALYSIS OF THE EXPIRED AIR

The expired air was collected in a series of Douglas bags, each collection lasting for a period of five minutes, both before and for varying

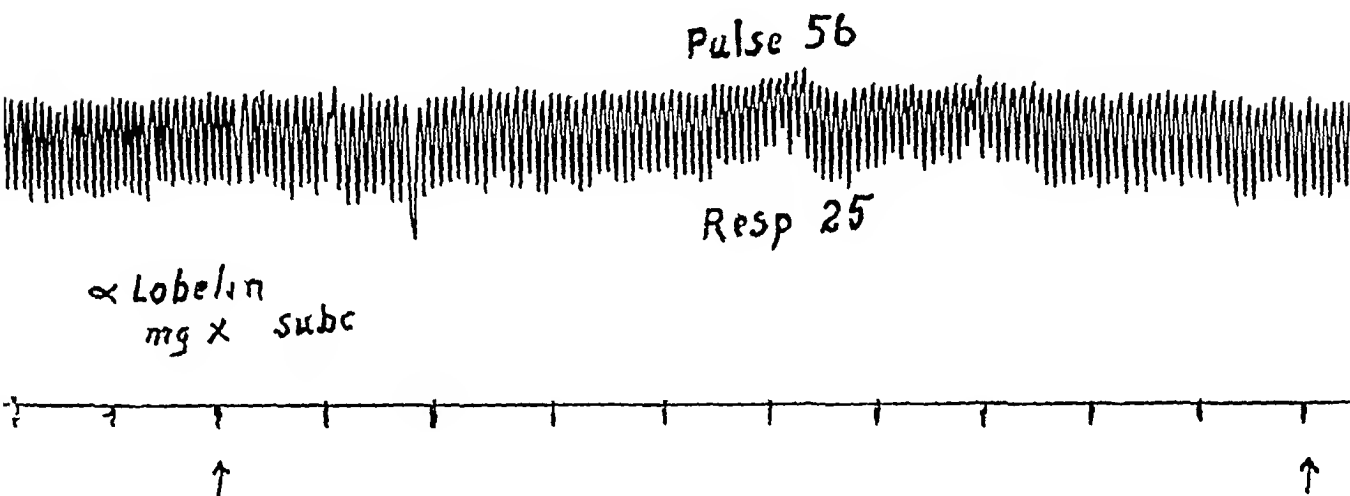


Chart 1—The respiratory excursion before and for five minutes following the administration of lobelin, time interval, thirty seconds

intervals after the administration of lobelin. The expired air showed, as a rule, first, a slight increase in carbon dioxide content, probably due to preliminary "washing-out" of this gas, which in turn was followed by a marked decrease in the percentage of carbon dioxide. The preliminary "washing-out" of carbon dioxide, when it occurred, occurred five or ten minutes after the drug was given, while the decrease was most marked after fifteen or twenty minutes. The percentage of oxygen in the expired air was found to be consistently increased, but on account of the increase in total ventilation more oxygen was, as a rule, inspired than before lobelin was given. The increase in carbon dioxide expired was always greater than the oxygen inspired, so that there was a constant increase in the respiratory quotient. This reached its maximum in about twenty minutes after the administration of the lobelin and then returned gradually to its previous level. At times, however, respiration was

affected unduly by nausea or vomiting. The results obtained from the analysis of the expired air in a series of eleven consecutive normal persons are shown in table 1.

EFFECT ON THE CARBON DIOXIDE CONTENT OF ARTERIAL BLOOD

The carbon dioxide content of the arterial blood at varying intervals after the administration of alpha lobelin showed a rather consistent decrease. In human beings, the average decrease in the carbon dioxide content of the arterial blood was 4.16 per cent by volume while in dogs it was 6.75 per cent by volume. The decrease started soon after lobelin was given and was still present in one instance at the end of an hour, showing that respiratory stimulation may be prolonged. The greatest decrease noted was in one of the dogs when it fell, at the end of fifteen minutes, from 59.7 per cent by volume to 50.3 per cent by volume. Twenty-five minutes later, it fell to 44.6 per cent by volume, probably being influenced by the dog's vomiting.

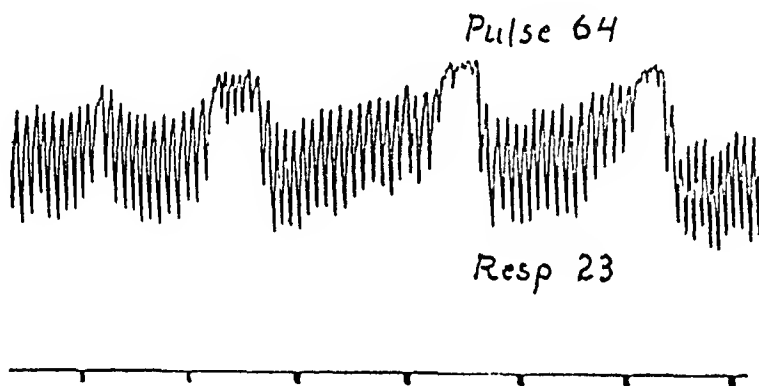


Chart 2—Chevne-Stokes type of respiration following the administration of alpha lobelin, time interval, thirty seconds.

INFLUENCE OF LOBELIN FOLLOWING SEDATIVES

The respiratory depressants used were morphine and chloral hydrate, sufficient being given to produce some respiratory depression as compared with the normal in each person. Whenever the respirations were depressed by this means, a definite stimulation was noted on the injection of lobelin, both as regards the total ventilation per minute and the depth of each respiration (table 2). The average increase in the ventilation of normal persons per minute as noted before was 31.25 per cent, but when depressed with one or the other drug, the same persons showed an average increase after injection of lobelin of 12.5 per cent, that is to say, still an appreciable amount. The volume of each respiration was also increased after injection on an average of 19.59 per cent, while in normal persons, the average was 14.98 per cent. The normal respiratory mechanism is, accordingly, easily and markedly stimulated by the admin-

istration of lobelin, and is so even during periods of respiratory depression. There was, furthermore, an increase of 11.17 per cent in oxygen consumption per minute when no sedatives were given but following their use the increase amounted to 2.72 per cent. In one uremic person whose respirations were only six per minute but who did not show cyanosis, 10 mg. of alpha lobelin was given intramuscularly. There was no appreciable change in the rate or character of the pulse; the respirations fell from six to five per minute, but no change could be noted in

TABLE 1—*Average Results of the Analysis of the Expired Air in Eleven Normal Persons*

No Preliminary Sedatives Five 5-Minute Periods	Pulse Rate per Min	Res- pira- tory Rate per Min	Volume per Minute Standard Temperature and Pressure Liters	Volume per Res- pira- tion Liters	Per Cent CO ₂ Pro- duced	Per Cent O ₂ Ab- sorbed	Res- pira- tory Quo- tient	O ₂ Ab- sorbed per Min., Liters	CO ₂ Pro- duced per Min. Liters
1 Volume 5 minute— 28.0 liters CO ₂ —2.91 per cent O ₂ —17.42 per cent	73	17	5.12	0.201	2.87	3.65	0.780	0.188	0.147
Alpha lobelin									
2 Volume 5 minute— 31.4 liters CO ₂ —2.72 per cent O ₂ —17.61 per cent	74	18	5.72	0.318	2.68	3.49	0.768	0.200	0.153
3 Volume 5 minute— 32.5 liters CO ₂ —2.95 per cent O ₂ —17.54 per cent	74	18	5.94	0.320	2.91	3.52	0.827	0.209	0.172
Five minute rest									
4 Volume 5 minute— 36.8 liters CO ₂ —2.57 per cent O ₂ —17.95 per cent	74	19	6.72	0.354	2.53	2.10	0.817	0.205	0.170
Ten minute rest									
5 Volume 5 minute— 31.3 liters CO ₂ —2.67 per cent O ₂ —17.60 per cent	73	18	5.87	0.326	2.63	3.52	0.748	0.205	0.154

their character. Ten minutes after the drug was given he became restless, vomited and perspired profusely. In all he was decidedly worse after treatment, and remained nauseated for twelve hours.

ILL EFFECTS ASSOCIATED WITH THE USE OF LOBELIN

The various American observers who have studied the use of lobelin have expressed a warning against the dangers associated with it and have done so rightly because it has been shown to possess a definite toxicity which interferes with its clinical value. Its administration as has been stated results in stimulation of the medullary centers which is not confined to the one for respiration but affects in an almost similar degree the near-by so-called, vomiting center. In the course of this

study, lobelin was given to twenty-five persons, twelve of whom became distinctly nauseated and ten vomited. This vomiting was severe and persisted in certain persons throughout the day. At no time was it possible to give twice the calculated physiologic dose without causing severe vomiting. The slowing of the pulse noted in one case can best be attributed to vagal stimulation. One adult who had never been nauseated nor vomited became ill following the injection of 10 mg., and vomited repeatedly for several hours. One of the dogs, also, which

TABLE 2—*Average Results of the Analysis of the Expired Air in Nine Persons Who Had Previously Been Given a Respiratory Depressant*

Preliminary Sedatives Five 5 Minute Periods	Pulse Rate per Min	Res- pira- tory Rate per Min	Volume per Minute Standard Temperature and Pressure, 1 liter	Volume per Res- pira- tion 1 liter	Per Cent CO ₂ Pro- duced	Per Cent O ₂ Ab- sorbed	Res- pira- tory Quo- tient	O ₂ Ab- sorbed per Min, 1 liter	CO ₂ Pro- duced per Min Liters
1 Volume 5 minute— 27.7 liters CO ₂ —3.13 per cent O ₂ —16.97 per cent	72	17	5.01	0.296	5.69	4.19	0.777	0.211	0.176
Alpha lobelin									
2 Volume 5 minute— 28.6 liters CO ₂ —3.02 per cent O ₂ —17.24 per cent	71	17	5.23	0.298	2.95	3.88	0.768	0.203	0.156
Volume 5 minute— 30.7 liters CO ₂ —3.02 per cent O ₂ —17.33 per cent	71	17	5.62	0.290	2.95	3.76	0.794	0.211	0.167
Five minute rest									
1 Volume 5 minute— 30.8 liters CO ₂ —3.02 per cent O ₂ —17.35 per cent	70	16	5.67	0.254	2.95	3.74	0.798	0.212	0.169
Ten minute rest									
5 Volume 5 minute— 28.2 liters CO ₂ —3.03 per cent O ₂ —17.00 per cent	69	15	5.18	0.245	2.99	4.18	0.715	0.217	0.155

had been given 5 mg. of the drug subcutaneously, started to vomit twenty minutes later, and refused to eat throughout the day. It had previously been in apparently good health.

Only one instance of severe collapse occurred. This followed about thirty seconds after the intramuscular administration of 10 mg. of lobelin and might have been caused by introducing the drug directly into a muscular vein. The man suddenly stopped breathing, became pale and was later cyanosed, the pulse rate fell from 78 to 60 per minute, the extremities became cold and bathed in profuse perspiration and he lay as in coma. After about forty-five seconds, the respirations began slowly to return. No other medication was given. He said that he had had a sudden sense of constriction or of great pressure on his chest and

had tried to breathe but had been unable to do so. He was severely nauseated, but did not vomit. This is probably an example of temporary paralysis of the respiratory center. To avoid this accident the drug should never be given intravenously.

ARGUMENT AND CONCLUSIONS

While alpha lobelin has been shown to be a definite stimulant to the respiratory center, there are certain features which are objectionable, and these suffice, I believe, to interfere with its use clinically. There has been shown an increase in the ventilation per minute after injection of lobelin. That this is not due solely to accelerated respiratory rate is evidenced by the fact that there is also an increase in the depth of each respiration. The increase in the respiratory volume is furthermore not merely transient, but commences as soon as the drug is administered, it persists and even after thirty-five minutes exceeds the volume before medication. The period of maximum effect comes in about fifteen or twenty minutes and falls back gradually to normal. The total ventilation in normal persons showed a greater increase than it did in those who had been given sedatives, while in the latter group there was a greater average percentage increase in the volume of each respiration.

The carbon dioxide content of the expired air showed a rather constant variation, first an increase probably due to a preliminary "washing-out" of that gas, and then a decrease, showing that the respiratory center was reacting to a lesser amount of carbon dioxide. The lowering of the amount of carbon dioxide in the arterial blood indicates that the threshold of the center has been definitely lowered.

The consistent increase in the amount of oxygen absorbed can be explained only by an increase in metabolic activity. This increase in oxygen consumption amounted, in normal persons, to 11.17 per cent and is indicative of an increase in metabolism consistent with increased muscular activity due to the respiratory stimulation. The increased utilization of oxygen is in itself not indicative of increased respiratory efficiency.

Unfortunately, stimulation of the medulla was not confined to the respiratory center, but affected in almost a similar degree the so-called vomiting center, and probably also the vagus centers. It is this associated action which makes the use of the drug undesirable, if not actually dangerous. Vomiting was fairly constant and severe—severe enough we believe, to balance its value as a respiratory stimulant. Vagus stimulation, shown by the lowered pulse rate, occurred in the case exhibiting the greatest toxic reaction. The drug should not be given intravenously because of the danger of temporary paralysis of the respiratory center, an accident which occurred once in this series of experiments. Lowering of the blood pressure after an injection of lobelin which others⁴ have

observed, is in itself an objectionable feature Vomiting or a lowering of the blood pressure in a person needing a respiratory stimulant are undesirable phenomena

CONCLUSIONS

- 1 Alpha lobelin is a definite stimulant to the respiratory center
- 2 Stimulation is confined not to that center alone, but affects the associated medullary centers in a like degree
- 3 The toxicity of the drug is so great that its extensive clinical use is inadvisable if not actually dangerous

TOXICITY OF NOVASUROL (MERBAPHEN)

ITS ACTION ON THE KIDNEY OF THE RABBIT

BENJAMIN I JOHNSTONE, M B

AND

H M KEITH, M B

DETROIT

This investigation was undertaken to study the toxicity of novasurol (merbaphen) by observing the lesions produced in the kidney of the rabbit following intravenous injection. Novasurol is an organic compound containing 33.9 per cent of mercury. It is the double sodium salt of oxymercuric orthochlorophenyloxy acetate and dimethylmalonyl urea, and it is prepared for use as a 10 per cent neutral sterile solution. It was first introduced by Bayer and Company as an antisyphilitic agent. Zeiler,¹ in 1917, was the first to describe its therapeutic use in this disease.

Soon after its introduction it was observed to have a marked diuretic effect, especially in those cases in which edema had developed. The fact that small doses of mercuric compounds produce a diuresis is not new. As early as 1800, it was known that the diuretic action of digitalis is enhanced when given in conjunction with mild mercuric chloride. This fact was also the basis for the famous Guy's pill. Mild mercuric chloride alone was shown by Jendrassik² to be capable of producing a marked diuresis when given in small doses. MacNider³ also recently showed that small doses of mercuric chloride produce diuresis. The early enthusiasm for mercuric compounds, however, waned as reports collected showed that a deleterious effect was produced on the kidney.

Novasurol is a more complex compound than those previously used and for this reason, is supposed to be less toxic. It is also freely soluble in water, and may be administered either by intramuscular or intravenous injection. This dose is reported to vary from 0.5 to 3 cc., with an average dose of 1 cc. for an adult, at intervals of from four to seven days. Oerting⁴ believes that nothing is to be gained by intravenous

From the Department of Medicine, Henry Ford Hospital

1 Zeiler, K. Novasurol ein neues Quecksilbersalz zur Syphilisbehandlung, mit Bemerkungen über die Grundsätze von Quecksilberhandlung, München med Wchnschr **64** 1257, 1917

2 Jendrassik, E. Das Calomel als Diureticum, Deutsches Arch f klin Med **38** 499, 1885-1886

3 MacNider, W de B. On the Elimination of Phenolsulphonephthalein in Acute Mercuric Chloride Intoxication, Proc Soc Exper Biol & Med **17** 73, 1920-1921

4 Oerting, H. Use of Novasurol as a Diuretic, Minnesota Med **8** 593, 1925

injection, but Evans⁵ stated that the addition of from 20 to 30 cc of 2 per cent saline to each dose of novasurol, if given intravenously, enhances the diuretic effect of the drug. Intravenous therapy also does away with the possibility of a local reaction at the site of injection. Saxl and Heilig⁶ reported the administration of doses of from 1 to 2 cc every other day for at least twelve injections. In 1920, these authors showed that it was valuable in cases of cardiac dropsy, and since that time it has become widely used.

Keith and Whelan⁷ described the effect of novasurol on the composition of the blood and the urine in cases of nephritis. Keith, Barrier and Whelan⁸ reported that in cases of nephritis with edema the combined effect of ammonium chloride, diet and novasurol produced beneficial results, but when considered singly, each factor might be ineffective. Rowntree, Keith and Barrier⁹ reported favorably on the use of this drug in cases of ascites due to hepatic disease, but the satisfactory results observed in this condition by these authors have not been uniformly obtained. Various authors deprecate its use in such cases. Saxl and Heilig⁶ reported some success with novasurol in cases of tuberculous pleurisy, peritonitis with effusion and in ascites secondary to carcinoma. Kulcke¹⁰ also obtained favorable results in cases of carcinomatosis and tuberculous effusions. Howarth¹¹ considered novasurol serviceable in cases of chronic nephritis with edema, but Crawford and McIntosh,¹² Oerting,¹³ Hubert,¹⁴ Rusznayak¹⁵ and Blum and Schwab¹⁶ were of the opinion that it is contraindicated in renal disease.

5 Evans, D. M. B. Novasurol and Hypertonic Saline in Chronic Oedema, *Brit. M. J.* **1** 739, 1926.

6 Saxl, P., and Heilig, R. Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, *Wien klin. Wchnschr.* **33** 943, 1920.

7 Keith, N. M., and Whelan, M. The Effect of Novasurol on the Composition of Blood and Urine, *Am. J. Physiol.* **72** 195, 1925.

8 Keith, N. M., Barrier, C. W., and Whelan, M. Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, *I. A. M. A.* **85** 799 (Sept. 12) 1925.

9 Rowntree, L. G., Keith, N. M., and Barrier, C. W. Novasurol in the Treatment of Ascites in Hepatic Disease, *I. A. M. A.* **85** 1187 (Oct. 17) 1925.

10 Kulcke, E. Novasurol als Diureticum, *Klin. Wchnschr.* **1** 622, 1922.

11 Howarth, R. Novasurol and Other Diuretics in Cardiac Oedema, *Brit. M. J.* **1** 186, 1926.

12 Crawford, J. H., and McIntosh, J. Observations on the Use of Novasurol in Oedema Due to Heart Failure, *J. Clin. Investigation* **1** 333, 1925.

13 Hubert, G. Erfahrungen mit Novasurol als Diureticum, *München med. Wchnschr.* **68** 1555, 1921.

14 Rusznayak, I. Orvosi hetil. **65** 443, 1921.

15 Blum, L., and Schwab, H. L'action diuretique des composés mercuriels, *Presse med.* **30** 1081, 1922.

Lambie,¹⁶ Gilchrist,¹⁷ Crawford and McIntosh,¹² Howarth,¹¹ Kulcke,¹⁰ Keith, Barrier and Whelan,⁸ Saxl and Heilig,⁶ Evans,⁵ and Oerting⁴ agreed as to the diuretic value of novasurol in cases of edema due to myocardial insufficiency, but considerable difference of opinion still exists as to its efficiency and the advisability of using it in cases of nephritis or in effusions due to cirrhosis, tuberculosis or carcinoma.

Occasionally such disagreeable symptoms as headache, vertigo, nausea, vomiting, stomatitis, diarrhea, fever and a rash are seen. These symptoms are estimated to occur in less than 1 per cent of cases, they are mild, and as a rule, result from the larger doses. They are generally transient and are not of sufficient intensity to require the discontinuance or interruption of the use of the drug, although this is sometimes necessary. Marcus¹⁸ reported a case in which marked hematuria followed the administration of novasurol so that the medication had to be stopped. Saxl and Heilig⁶ claimed that disagreeable symptoms occur most often in emaciated persons, particularly if they are constipated. Redlich¹⁹ reported three cases in which death followed the administration of novasurol, in one case, death occurred after two doses with a three day interval between them, and in one case death was due to enteritis and volvulus following a dose of 1 cc given three weeks previously.

Most writers stated definitely that as evidenced by clinical observation and microscopic examination of the urine, no effect on the kidney was noted.

The exact way in which novasurol brings about diuresis has not been established, but Keith and Whelan,²⁰ and Crawford and McIntosh¹² believed it to be by a combined action on the kidney and the extra-renal tissues. Bohn²¹ agreed with this, but believed that the extra-renal mobilization of fluid is the more important. Saxl and Heilig²² also considered that the action is mainly extra-renal, contrasting it with the action of uranium in which no increased excretion of salt occurs. On the other hand, Blum and Schwab¹⁵ believed the effect is due to action

16 Lambie, C. G. Novasurol and Other Diuretics in Cardiac Oedema, *Brit M J* **1** 80, 1926.

17 Gilchrist, A. R. Novasurol. A New Diuretic, *Lancet* **2** 1019, 1925.

18 Marcus, S. Experience with Novasurol, *Canad M A J* **16** 690, 1926.

19 Redlich, F. Letale Quecksilberintoxikation nach einmaliger Novasurol-injektion, *Wien klin Wchnschr* **38** 359, 1925.

20 Keith, N. M., and Whelan, M. A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J Clin Investigation* **3** 149, 1926.

21 Bohn, H. Fortgesetzte Studien über Novasurol, seine Wirkung bei verschiedenen Lebensaltern und bei Diabetikern sowie sein etwaiger Einfluss auf Ionenverschiebungen im Organismus. *Deutsches Arch f klin Med* **143** 225, 1923.

22 Saxl, P., and Heilig, R. Ueber die Novasurol-diurese, *Ztschr f d ges exper Med* **38** 94, 1923.

on the renal tissues only Jackson²³ has shown that changes in volume occur in the kidney after the injection of novasurol, he considered the diuretic action to be related to vascular changes possibly causing greater contraction in the efferent than in the afferent glomerular capillaries

MATERIALS AND METHOD

Thirty-two animals were used. They were first weighed and the drug introduced slowly into the marginal vein of the ear. A 10 per cent neutral sterile solution prepared by the Winthrop Chemical Company was used. It was diluted before injection with sterile physiologic sodium chloride, various dilutions being employed.

Though the rabbits were carefully weighed, the drug was not given according to the weight in kilograms as it was at first thought that the tolerance per rabbit might be more nearly similar than the tolerance per kilogram. It was found that this was not true as the degree of damage varied closely with the amount of novasurol given per kilogram.

For the purposes of this study, the animals were divided into six groups as follows:

Group I Four rabbits, killed with massive doses of the drug, kidneys not studied.

Group II Three rabbits, killed with massive doses of the drug, kidneys studied.

Group III Four rabbits, given repeated doses of 0.1 cc. at intervals of about four days until death.

Group IV Four rabbits, given repeated doses of 0.2 cc. at intervals of about four days until death.

Group V Eight rabbits, given doses varying from 0.1 cc. to 0.8 cc. per rabbit and killed twenty-four hours later.

Group VI Nine rabbits, each given 0.2 cc. of novasurol irrespective of the body weight and killed in five minutes, one hour, four hours, sixteen hours, two days, four, six, ten and fourteen days, respectively.

The details regarding each group have been summarized in tables 1 to 6.

The animals in groups I, II and III, with the exception of rabbit 13, died from the effect of the drug, this animal was killed by a blow on the head. In group IV rabbit 12 died from the effects of the drug, rabbit 16 from intestinal obstruction, while rabbits 2 and 3 were killed by a blow on the head six weeks after the last dose of novasurol. All the rabbits in group V were killed within two minutes by giving them a little ether and then a blow on the head. Those in group VI were killed by a sudden blow on the head.

Rabbits 5, 9, 12 and 16 died between midnight and 8 a. m., and were autopsied at 8 a. m. Rabbit 11 died at 1 p. m. and was kept in the icebox until examination could be made at 5 p. m. the same afternoon. All other rabbits were autopsied in from five to thirty minutes, postmortem.

Small strips of tissue were removed from different areas of each kidney. The sections were preserved in 10 per cent formaldehyde, then dehydrated, fixed in paraffin, sectioned and stained with hematoxylin and eosin.

23 Jackson, D. E. The Pharmacological Action of Mercury in Organic Compounds, *J. Pharmacol. & Exper. Therap.* **29**: 471, 1926.

GENERAL DESCRIPTION OF EXPERIMENTAL RESULTS

In groups I and II, an attempt was made to determine the immediate lethal dose of the drug. The rabbits in these groups received massive doses which varied from 0.733 to 0.168 cc per kilogram. Rabbits 6 and 8, which received 1.6 and 1.5 cc, respectively, or 0.586 and 0.733 cc per kilogram, died within three minutes in convulsions. Rabbit 1 received 1.5 cc intravenously without evidence of immediate effect. This rabbit was large and the dose amounted only to 0.366 cc per kilogram. Ten minutes later, the rabbit appeared to be normal. It was then given 1.5 cc intramuscularly and died ten minutes later. This rabbit received 0.732 cc per kilogram in all. Rabbit 9, which received 1.5 cc, or 0.629 cc per

TABLE 1—Group I Single Doses Producing Death

Rabbit Series Number	Weight, kg	Dose of Novasurol per Kilo- gram, Cc	Amount of Physiologic Sodium Chloride Num- ber of Dose, Cc Doses		Total Amount Novasurol Received, Cc 1.51 M	Length of Life After Treatment	Equivalent Dose for Man Weighing Seventy Kilo- gram, Cc	Kidney Damage	
								Gross	Microscopic
1	4.09	0.732	10	within 10 min	1.51 V 3	23 min	51.24	No Study	No Study
4	2.4	0.168	2	1	0.4	4 days	11.76	No Study	No Study
6	2.7	0.586	3	1	1.6	3 min	41.02	No Study	No Study
8	2.04	0.733	5	1	1.5	3 min	51.33	No Study	No Study

TABLE 2—Group II Single Doses Producing Death

Rabbit Series Number	Weight, Kg	Dose of Novasurol per Kilogram, Cc	Amount of Physi- ologic Sodium Chloride, per Dose, Cc	Number of Doses	Total Amount of Novasurol Injected, Cc	Length of Life After Beginning Treat- ment	Equivalent Dose for Man Weighing Seventy Kilograms, Cc	Kidney Damage *	
								Gross	Microscopic
5	2.28	0.352	4	1	0.8	84 hrs	21.6	+++++	+++++
7	2.33	0.324	5	1	1.0	86 hrs	22.68	+++++	+++++
9	2.33	0.629	5	1	1.5	14 hrs	44.03	+++++	+++++

* The severity and extent of the kidney change is represented as varying from 0 to 10 + s

kilogram, although it appeared ill immediately, did not die for fourteen hours. Rabbits 5 and 7 each received similarly sized doses, namely, 0.352 cc and 0.324 cc per kilogram, and died in eighty-four and eighty-six hours, respectively. Rabbit 4 was given a dose of 0.168 cc per kilogram and died in four days. No rabbit receiving 0.168 cc or over recovered. This would be equivalent to about 12 cc intravenously for a man weighing 70 Kg. Rabbits receiving about 0.7 cc per kilogram died suddenly in convulsions. This dose would approximate 50 cc intravenously for a man weighing 70 Kg. Rabbit 6 died suddenly after a dose of 0.586 cc per kilogram. This animal, however, received 1.6 cc, but was a relatively large rabbit.

When massive doses were given, of those animals that did not die suddenly, those that received the larger doses died more quickly. Rabbit 9 died in fourteen hours after a dose of 0.629 cc per kilogram, rabbit 5 in eighty-four hours after a

dose of 0.352 cc per kilogram, rabbit 7 in eighty-six hours after a dose of 0.324 cc per kilogram, and rabbit 4, in ninety-six hours after a dose of 0.168 cc per kilogram

The most extensive damage to the kidney was observed in group II. Rabbits receiving the largest dose per kilogram did not necessarily show the most severe degeneration as the time over which the poison acted was an important factor. Rabbit 9, although it received a dose approximately twice as large per kilogram as did rabbits 5 or 7, showed less marked damage to the kidney. Rabbit 9, however, lived only fourteen hours and rabbits 5 and 7 lived eighty-four and eighty-six hours, respectively. Evidence of regeneration was seen in rabbits 5 and 7 which was not present in rabbit 9.

In group III, rabbit 11 died two days following the fifteenth dose. A small amount of acute degeneration was present as well as evidence of slight chronic change represented by cysts, infiltration with lymphocytes and an increase in connective tissue. Rabbit 13 received twenty-eight doses and was clinically well at the end of six months. It was killed six weeks after the last dose of novasurol. Acute degeneration was not seen, but small areas of infiltration and a slight

TABLE 3—Group III Repeated Doses of 0.1 Cc Until Death

Rabbit Series Number	Weight, kg	Dose of Novasurol per kilogram, Cc	Amount of Physiological Sodium Chloride, per Dose, Cc	Number of Doses	Total Amount of Novasurol Injected, Cc	Length of Life After Beginning Treatment	Equivalent Dose for Man Weighing Seventy Kilograms, Cc	Kidney Damage	
								Gross	Microscope
11	3.09	0.032	0.5	15	1.5	2 mos	2.24	0	—
13	2.4	0.011	0.5	28	2.8	6 mos (killed)	3.62	0	—
14	2.59	0.038	0.5	5	0.5	3 wks	2.66	—	—
15	1.9	0.053	0.5	1	0.4	3 wks	3.71	—	—

increase in connective tissue as well as an occasional cyst were present. Rabbit 14, although it received a smaller dose than rabbit 13, namely, 0.038 cc per kilogram, succumbed after five doses and rather extensive degeneration was found in the kidneys. Rabbit 15 died after four doses, the dosage totaled 0.053 cc per kilogram, and hence is considered relatively large. Relatively little damage was found in the section labeled 15. This does not fit in with the picture that one would expect to find, as rather extensive degeneration would be surmised. One is led to suspect that an error was made in labelling this kidney.

In group IV, rabbits 2 and 3 received relatively large doses, namely, 0.061 and 0.077 cc per kilogram for twenty-three doses over a period of six months. Each of these animals appeared normal in every way when killed six weeks after the last dose. On examination of their kidneys, a small amount of scarring was seen. Rabbit 12 received a still larger dose, namely, 0.09 cc per kilogram and died in one month after five doses. Considerable degeneration was found in the kidney. Rabbit 16 of this group died of intestinal obstruction and peritonitis, the etiology of which was not determined. This animal could not be used in this study as it could not be proved that the novasurol had anything to do with the obstruction and peritonitis.

The animals in group V were arranged in an attempt to show the effect of different sized doses at the end of twenty-four hours. The animals were thus

given doses ranging from 0.1 cc to 0.8 cc a rabbit. It was hoped to see the effect of gradually increasing doses. The animals, however, varied in weight, and the degeneration was seen to vary directly as the dose per kilogram rather than as the dose per rabbit. Thus, rabbits 17, 18, 19 and 20 received gradually increasing doses per rabbit, and also per kilogram, and the damage was gradually more marked in order. However, though rabbits 20, 21 and 22 received increasing doses per rabbit, they received similar doses per kilogram. The sections made from the

TABLE 4—Group IV Repeated Doses of 0.2 Cc Until Death

Rabbit Series Number	Weight, kg	Dose of Novasurol, per kilogram, Cc	Amount of Physiological Sodium Chloride, per Dose, Cc	Number of Doses	Total Amount of Novasurol Injected, Cc	Length of Life After Beginning Treatment	Equivalent Dose for Man Weighing Seventy kilograms, Cc	Kidney Damage	
								Gross	Microscopic
2	3.3	0.061	1	23	4.6	7 mos (killed)	4.22	0	—
3	2.6	0.077	1	23	4.6	7 mos (killed)	5.39	0	—
12	2.16	0.099	1	5	1.0	1 mon	6.3	—	—
16	3	0.066	1	15	3.0	2 mos	4.62	—	—
									Spontaneous chronic nephritis

TABLE 5—Group V Single Doses from 0.1 to 0.8 Cc Killed in Twenty-Four Hours

Rabbit Series Number	Weight, kg	Dose of Novasurol per kilogram, Cc	Amount of Physiological Sodium Chloride, per Dose, Cc	Number of Doses	Total Amount of Novasurol Injected, Cc	Length of Life after Beginning Treatment	Equivalent Dose for Man Weighing Seventy kilograms, Cc	Kidney Damage	
								Gross	Microscopic
17	1.14	0.089	0.5	1	0.1	24 hrs	6.23	0	0
18	2.0	0.135	1.0	1	0.2	24 hrs	9.45	—	—
19	1.0	0.291	1.5	1	0.3	24 hrs	20.31	—	—
20	1.14	0.352	2.0	1	0.4	24 hrs	24.64	—	—
21	1.6	0.314	2.5	1	0.5	24 hrs	21.98	—	—
22	1.8	0.333	3.0	1	0.6	24 hrs	23.31	—	—
23	1.8	0.335	3.5	1	0.7	24 hrs	26.95	—	—
24	2.16	0.370	4.0	1	0.8	32 hrs	25.90	—	—

kidneys of these three rabbits were similar. Rabbits 23 and 24 received doses of much the same size. A similar degree of damage to the kidney was noted, though the degeneration was more marked than in rabbits 20, 21 and 22. Although the dose was somewhat smaller in rabbit 24 than in 23, the former was not killed for thirty-two hours.

The rabbits in group VI were given relatively large doses, though the amounts would not be considered lethal in the average animal. None of the animals in this series died from the effect of the drug. They were killed at intervals varying from five minutes to fourteen days as shown in table 6. The earliest changes were seen in one hour and these grew progressively more extensive with the doses used.

up to two days. In four days, very few of the tubules showed acute degeneration and evidence of regeneration was seen. From this time on signs of acute degeneration gradually disappeared and little evidence of an acute process was present at ten days. Here, extensive evidence of regeneration was seen. In fourteen days there was less evidence of active regeneration.

Pathologic Observations—Gross. If the changes were slight as observed histologically, either due to a small dose or to the fact that a massive dose had been acting a short time, little abnormality could be made out in the gross appearance. The earliest departure from the normal was seen at the end of four hours in a rabbit that was given a dose of about 0.12 cc. At this time the capsule stripped easily, the surface was smooth and glistening, the superficial veins were injected and the uncut kidney as well as the cut surface was reddish or grayish. The cut margins did not evert. In sixteen hours after a dose of 0.098 cc per kilogram, the external surface had become pale with fine mottling. The cut margins everted slightly and the cortex was paler than normal. Up to this time

TABLE 6—Group VI Dose of 0.2 Cc and Killed at Intervals from Five Minutes to Fourteen Days

Rabbit Series Number	Weight, kg	Dose of Novasurol per Kilogram, Cc	Amount of Physio logic Sodium Chloride, per Dose, Cc	Number of Doses	Total Amount of Novasurol Injected, Cc	Length of Life After Beginning Treatment	Equivalent Dose for Man Weighing Seventy Kilograms, Cc	Kidney Damage	
								Gross	Microscopic
25	1.6	0.125	1.0	1	0.2	5 min	8.7	0	0
26	1.48	0.135	1.0	1	0.2	1 hr	2.45	0	+
27	1.82	0.110	1.0	1	0.2	4 hrs	7.7	+	++
28	1.14	0.098	1.0	1	0.2	16 hrs	6.85	+	++
29	1.70	0.118	1.0	1	0.2	2 days	8.26	++	+++
30	1.82	0.110	1.0	1	0.2	4 days	7.7	+++	+++
31	1.82	0.110	1.0	1	0.2	6 days	7.7	+++	+++
32	1.03	0.103	1.0	1	0.2	10 days	7.21	+++	+++
33	1.82	0.110	1.0	1	0.2	14 days	7.7	+++	+++

there was little change in size or weight. In two days after a dose of 0.118 cc per kilogram, the kidneys were enlarged and of a soft consistency. The capsule stripped easily. The surface was smooth and of a grayish or grayish white color. On cut section, the margins readily everted and the pale grayish swollen cortex stood out from a pale or slightly reddish medulla. The appearance in the gross remained similar, except for a change in size, until death. If the rabbit recovered, by the sixth day there was less eversion of the cut margin, and between the sixth and tenth days, the kidneys began to decrease somewhat in size. By the tenth day, the knife grated against calcium and the cortex appeared less swollen. There was no eversion of the cut margin. By the fourteenth day, the kidneys were much less swollen and were a pale yellowish red, there was no eversion of the cut margin and the medulla and cortex were poorly demarcated.

Microscopic. The characteristic lesion seen microscopically throughout the sections showing change was a degeneration of the epithelium lining the renal tubules. The earliest stage of such degeneration was seen in rabbit 26 one hour after receiving a dose of 0.135 cc per kilogram. Under the low power magnification, a few scattered areas were seen which stood out from the rest of the tissue, in that they took the acid stain more deeply. These areas, for the most part, were

situated immediately beneath the capsule and were small and in close proximity to malpighian bodies. Under the high power magnification they were seen to be areas of proximal convoluted tubules the cells of which showed varying degrees of swelling, some obliterating the lumen. In these cells the outline was less distinct than normal and often lost. Many showed vacuolization. The nuclei showed either pyknosis, karyorrhexis or were not visible. Degeneration was not

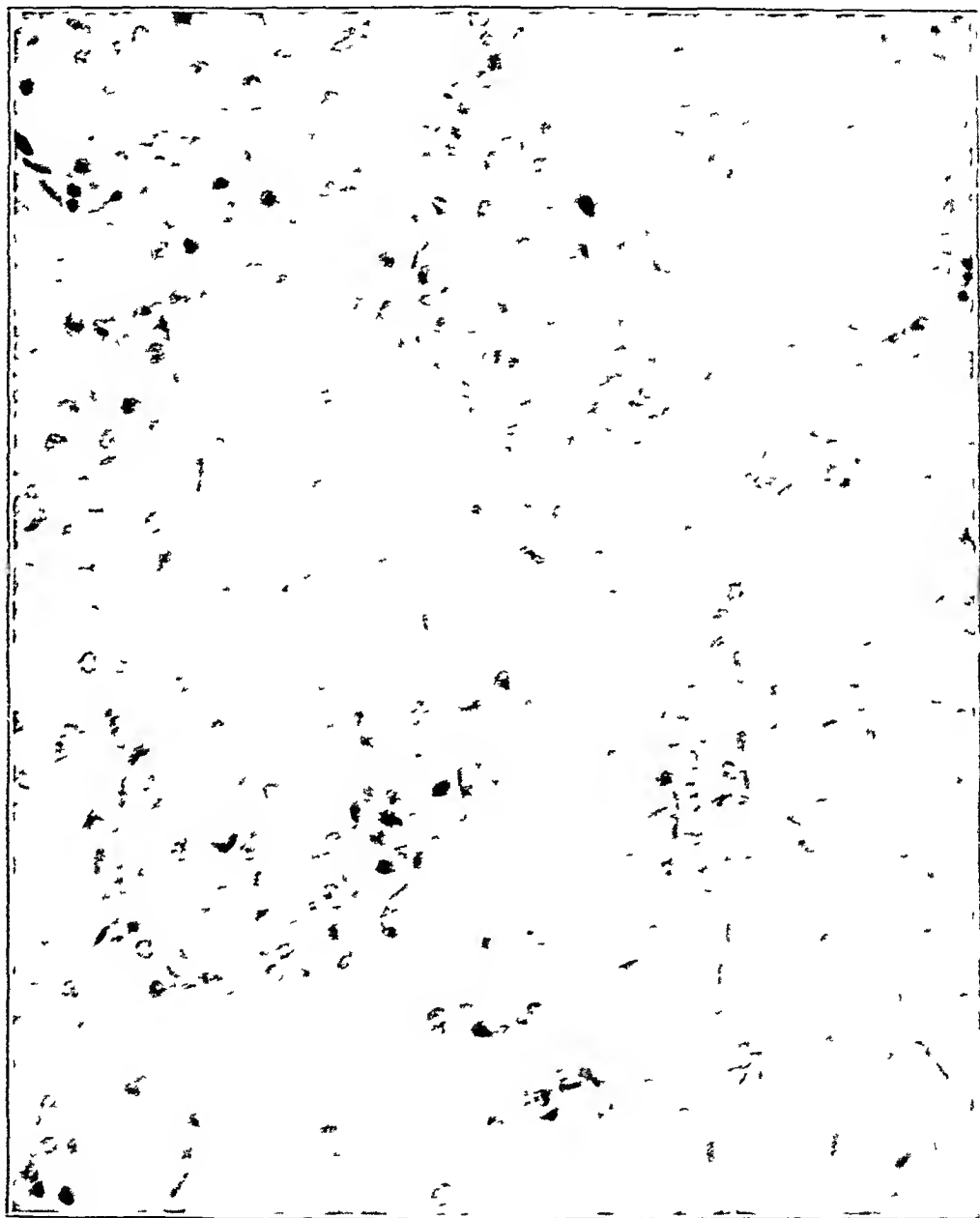


Fig 1.—Section from the kidney of rabbit 26 which received 0.135 cc of novasurol per kilogram and was killed in one hour. Definite but early degeneration is seen in scattered areas of proximal convoluted tubules. Photomicrograph, 16 mm obj.

observed elsewhere in the kidney at this stage (fig 1). In four hours following a dose of 0.11 cc per kilogram the degeneration was more extensive and more advanced (fig 2). Pyknotic nuclei were striking in this section. By this time, some of the ascending limbs of Henle showed early degeneration but the greater

part of the lesion was still confined to the convoluted tubules, situated in the vicinity of the kidney capsule. In many of these cells the nuclei had disappeared, the cell had begun to disintegrate and the structure of the tubule was partially lost. In sixteen hours following a dose of 0.098 cc per kilogram, about one third of the number of the convoluted tubules had undergone complete necrosis (fig. 3). These tubules were represented by a structureless, granular but otherwise homo-

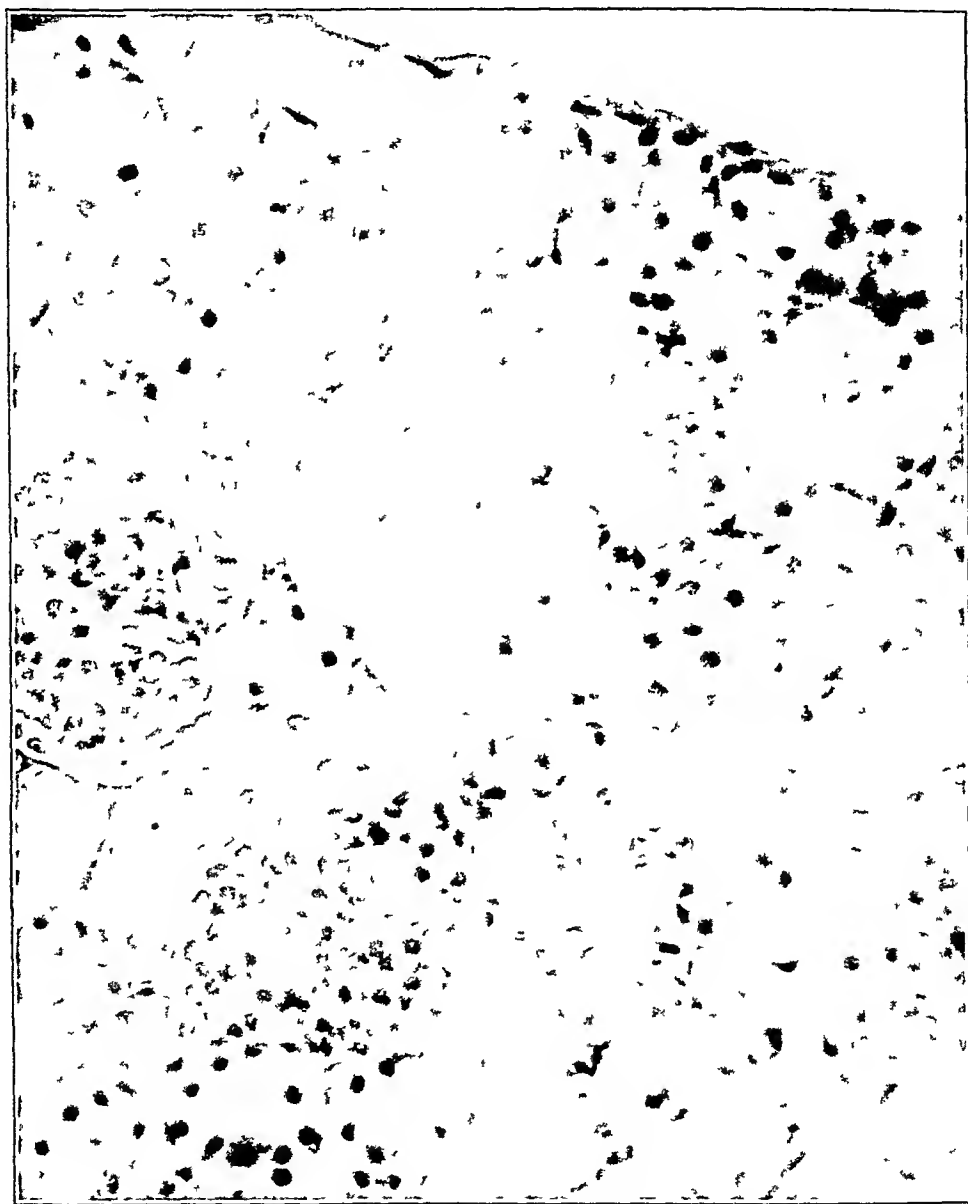


Fig. 2—Section from the kidney of rabbit 27 which received 0.11 cc of novasurol per kilogram and was killed at the end of four hours. Degeneration is more extensive than in figure 1, and in some tubules is further advanced. Pyknotic nuclei are striking in some tubules. Photomicrograph 16 mm obj.

geneous pinkish staining mass devoid of nuclei. About one quarter of the number of the ascending limbs of Henle showed similar complete necrosis. A few of the convoluted tubules were unaffected, but the majority showed various stages of change.

The most severe and extensive degeneration was present in sections from rabbits 5 and 7 (fig 4). Practically all the proximal convoluted tubules and the majority of the distal convoluted tubules and the ascending limbs of Henle had undergone complete necrosis, being represented by the characteristic pinkish staining structureless mass. Normal convoluted tubules were not seen. A few were present showing early degeneration, the cells were swollen and the nuclei



Fig 3—Section from the kidney of rabbit 28 which received 0.098 cc of novasurol per kilogram and was killed at the end of sixteen hours. Degeneration is still further advanced and more extensive than in figure 2. Some tubules have undergone complete necrosis. Photomicrograph, 16 mm obj.

normal or pyknotic. Many cells showed vacuolization. Degeneration was not seen in the connecting or collecting tubules or papillary ducts.

When the dose was sublethal, the degeneration was less severe, and as the animal began to recover there was less evidence of complete necrosis. In rabbit 30,

killed four days after the injection of 0.11 cc per kilogram, few of the convoluted tubules showed the complete necrosis that was present in rabbit 7 or even in rabbit 29 killed at the end of two days (fig 5). About one third of the number of ascending limbs of Henle still showed complete degeneration. In rabbit 31, killed at the end of six days, there were only a few convoluted tubules and ascending limbs of Henle showing complete necrosis (fig 6). Tubules were

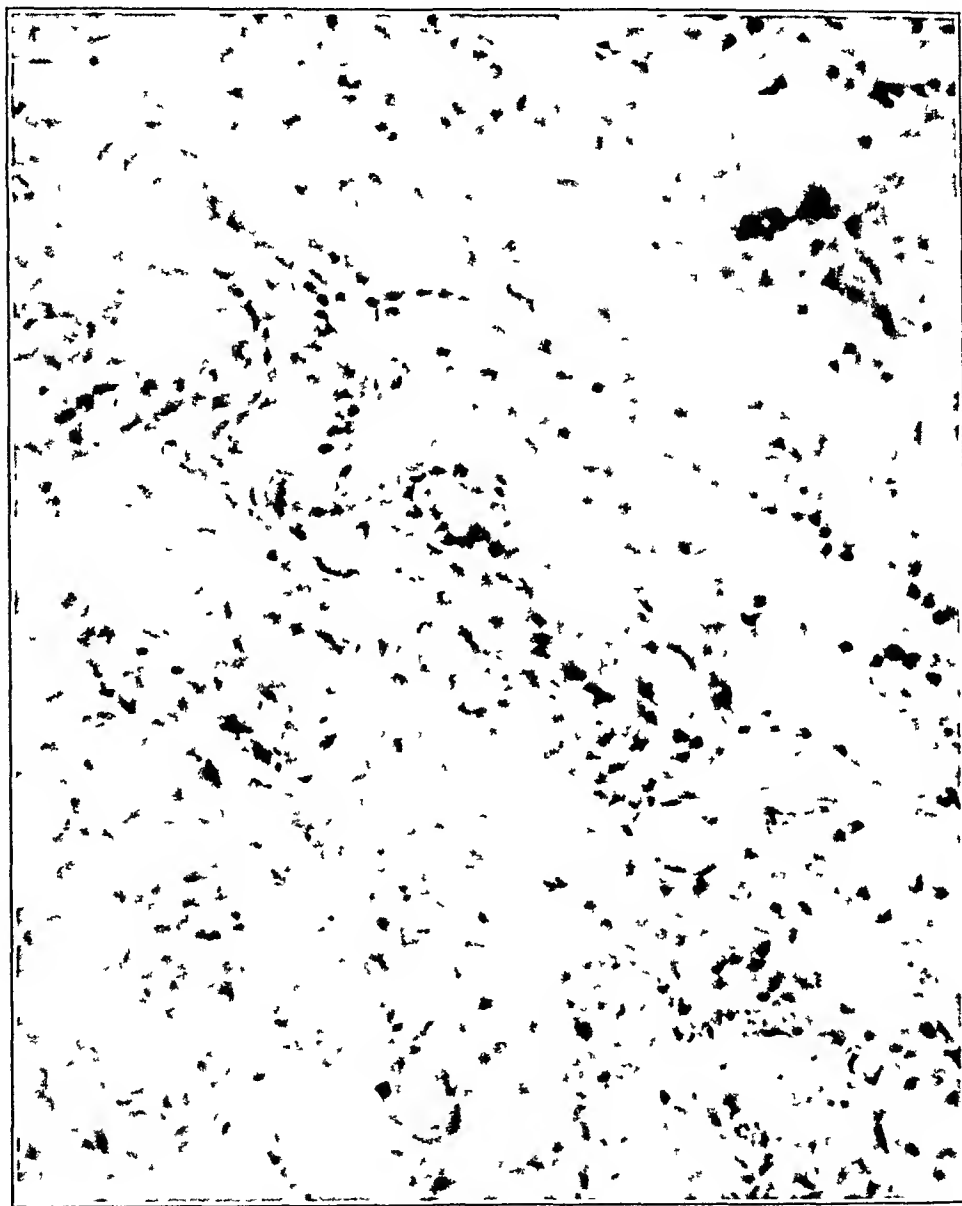


Fig 4—Section from the kidney of rabbit 7 which received 0.324 cc of novasurol per kilogram and died in eighty-six hours. There is almost complete degeneration of the convoluted tubules and the ascending limbs of Henle. Considerable evidence of regeneration is present. Photomicrograph, 16 mm obj.

present, however, in various stages of less severe degeneration. In ten days following a dose of 0.103 cc per kilogram, little evidence of acute degeneration was seen (fig 7). Degeneration was accompanied by detritus in the lumina of the tubules

and the presence of casts. This was most abundant when the acute degeneration was at its height.

In those animals that survived more than three days, evidence of regeneration was seen and this became more extensive and advanced in proportion to the length of time the animal lived after the treatment. Rabbits 5 and 7 lived eighty-four hours and eighty-six hours, respectively, and evidence of regeneration of the cells

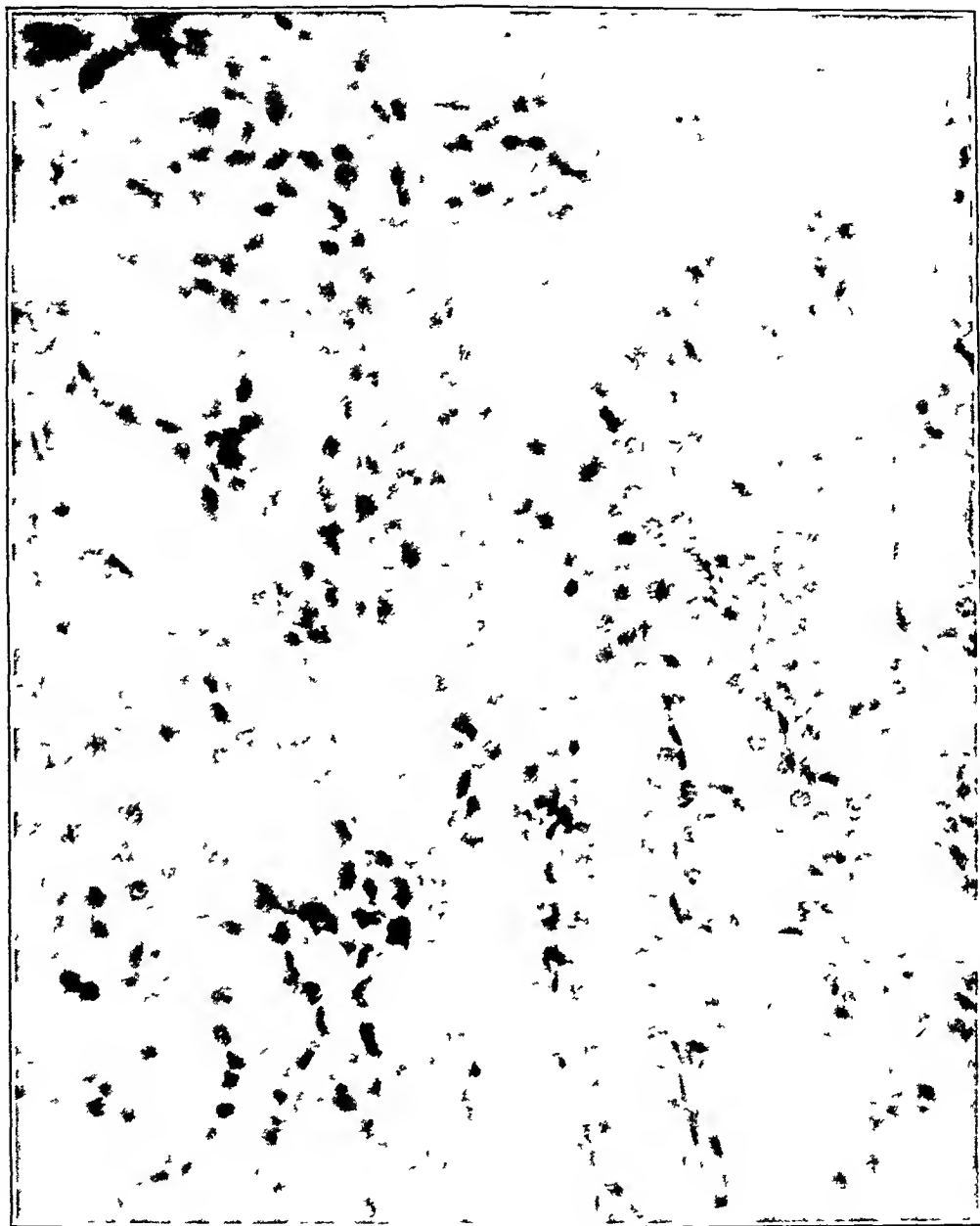


Fig 5—Section from the kidney of rabbit 30 which received 0.11 cc of novasurol per kilogram and was killed at the end of four days. Acute degeneration has been less extensive and there is considerable evidence of regeneration. Photomicrograph, 16 mm obj.

lining the renal tubules was present in each. In sections from these animals, a considerable number of the ascending limbs of Henle and the convoluted tubules appeared bluish under the low power magnification (figs 4 and 8). These were seen to be syncytial masses containing many deeply staining vesicular nuclei or

tubules lined by flat, irregularly round or polygonal cells with characteristic nuclei. The cytoplasm of these cells was stained somewhat bluish and occasionally mitotic figures were seen. This picture is described by MacCallum²⁴ as being characteristic of regeneration in acute poisoning from mercuric chloride.

Similar evidences of regeneration were present in rabbit 30 four days after treatment. The dose given to this rabbit was much smaller than that given to

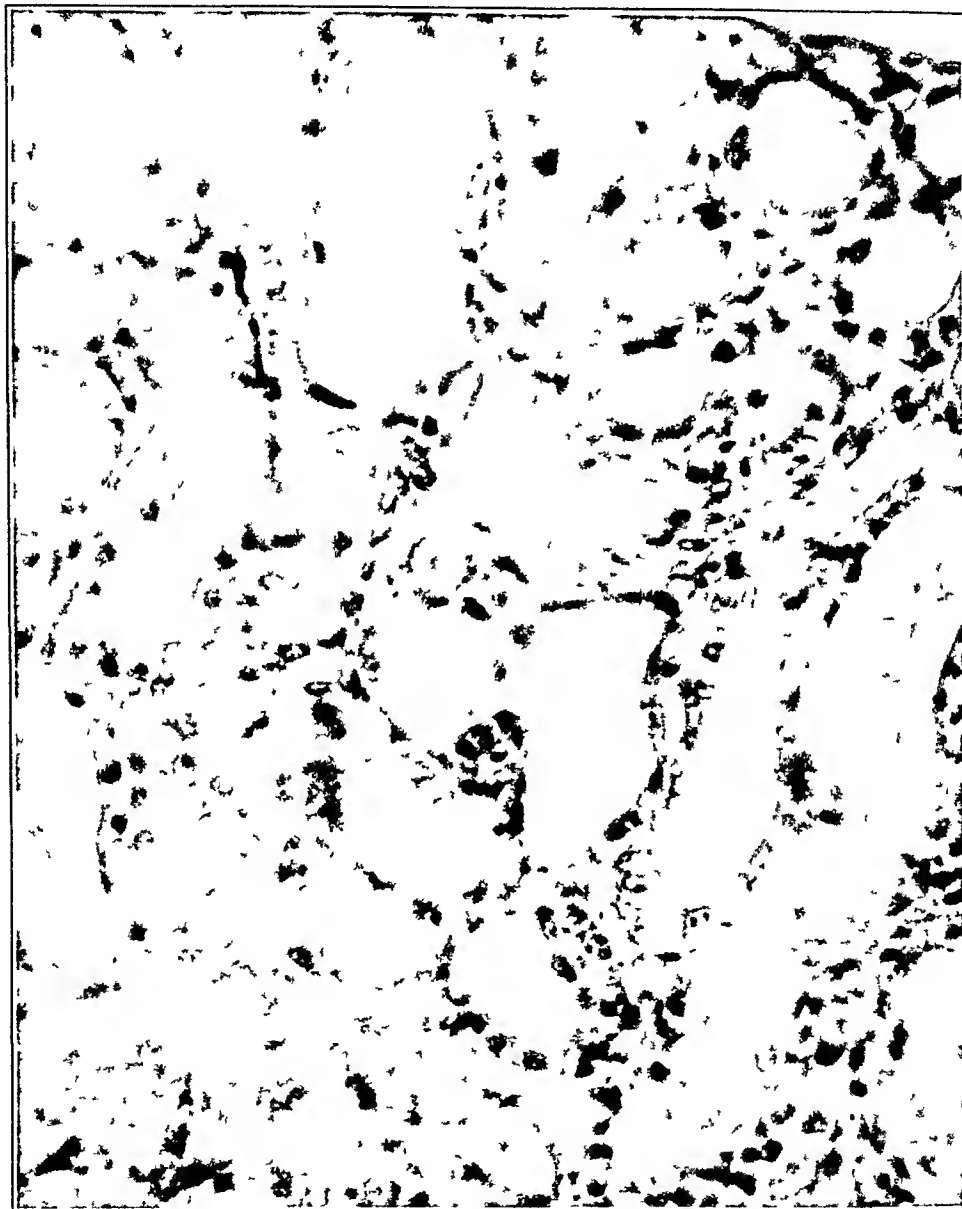


Fig. 6—Section from the kidney of rabbit 31 which received 0.11 cc. of novasurol per kilogram and was killed at the end of six days. Extensive evidence of active regeneration is present. Photomicrograph, 16 mm. obj.

rabbits 5 or 7 and this animal had begun to recover. In the section the newly growing cells in many cases surrounded the necrotic mass representing the

²⁴ MacCallum, W. G. *A Text-Book of Pathology*, ed. 2, Philadelphia, W. B. Saunders Company, 1922, pp. 404-406.

destroyed tubule. In rabbit 31, killed six days after receiving the drug, signs of regeneration were the predominating feature (figs 6, 9 and 10). The few tubules still showing complete necrosis were for the most part surrounded by actively proliferating young cells. Many of the tubules were lined by flattened epithelium with more or less normal nuclei and cytoplasm. Many were replaced by syncytial masses or lined by irregularly shaped cells with bluish staining cytoplasm and large



Fig 7—Section from the kidney of rabbit 32 which received 0.103 cc of novasurol per kilogram and was killed at the end of ten days. There is evidence of rather extensive deposition of calcium. Photomicrograph, 16 mm obj.

vesicular nuclei, some of which showed mitotic figures. At the end of ten days, in sections from rabbit 32, the majority of the tubules were lined by flattened epithelium. There was little evidence of actively proliferating young cells. In rabbit 33 at the end of fourteen days, only an occasional young cell was seen, but the epithelium for the most part was flatter than normal.

The earliest evidence of calcium deposition was seen in rabbit 30 four days after the injection of the drug. It was located in the debris of the convoluted tubules. The amount was small and for the most part irregularly scattered throughout the subcapsular portion of the cortex. In rabbit 31 at the end of six days, a slightly larger amount of calcium was present, while in rabbit 32 killed at the end of ten days, the striking feature was the large amount of bluish material

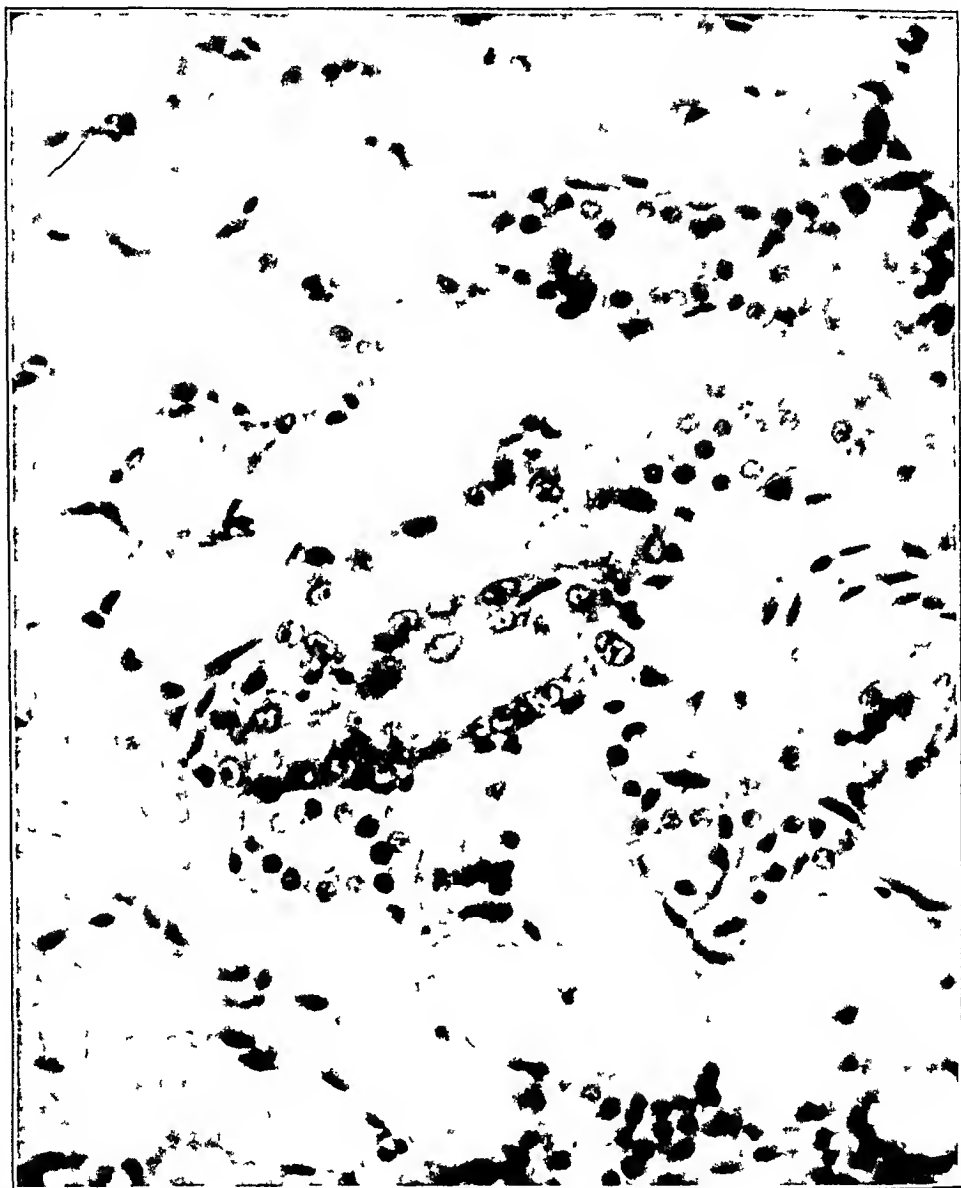


Fig 8—Section from the kidney of rabbit 7 which received 0.324 cc of novasurol per kilogram and died in eighty-six hours. In the center of the photograph are seen cross-sections of convoluted tubules lined by irregular cells with large vesicular nuclei and bluish-staining cytoplasm. Photomicrograph, 16 mm obj.

infiltrating the debris (fig 7). In some cases, masses of calcium were surrounded by actively proliferating cells. A small amount of calcium was seen in the ascending limbs of Henle. None was seen in the glomeruli. There was much less calcium present in rabbit 33 killed at the end of fourteen days than in rabbit 32 killed at the end of ten days.

The glomeruli were normal throughout except in two animals. Rabbit 16 showed the typical picture of a chronic nephritis, and in rabbit 5, many of the glomeruli showed acute change. In the latter, detritus was seen in the capsular spaces of many of the malpighian bodies in some instances, crowding the glomerular tuft to one side. This detritus consisted of red blood cells, white blood cells and a homogeneous pinkish staining material. Glomeruli were not



Fig 9—Section from the kidney of rabbit 31 which received 0.11 cc of novasurol per kilogram and was killed at the end of six days, high power magnification showing young flattened cells with large irregular vesicular nuclei lining a proximal convoluted tubule. Photomicrograph 4 mm obj.

observed in this section to show increased cellularity or change in Bowman's capsule.

Except for medullary hyperemia in the acute stages, the vessels were normal throughout. The cortex was consistently anemic. There was considerable inter-

stitial edema in the acute stages and in rabbits 5 and 7, an occasional small nest of lymphocytic infiltration was seen in the interstitial tissue

In rabbits 2, 3 and 13, which received relatively large amounts of novasurol over a period of six months, the pathologic changes were slight. Rabbit 2 showed the epithelial lining of the convoluted tubules to be somewhat flatter than normal. A few small retention cysts and areas of lymphocytic infiltration were present



Fig 10—Section from the kidney of rabbit 31 showing a mass of nuclei without evidence of cell boundary. These fill the space formerly occupied by a convoluted tubule. These nuclei are large, vesicular and vary a good deal in size, the cytoplasm stains bluish. Photomicrograph, 4 mm obj.

There was a slight increase in connective tissue in localized areas. Rabbits 3 and 13 showed similar evidence of chronic change (figs 11, 12 and 13).

Rabbit 16 showed the typical picture of a chronic nephritis (fig 14). The interstitial tissue was increased, the glomeruli closely packed together and in many

instances, Bowman's capsule was considerably thickened. A moderate degree of acute degeneration was also present and a small amount of calcium. This section showed the presence of a chronic nephritis with a superimposed acute degeneration. This animal died from intestinal obstruction and peritonitis. The picture could not be said to be due to novasurol and was most likely a spontaneous nephritis commonly seen in rabbits. The acute degeneration was probably partially

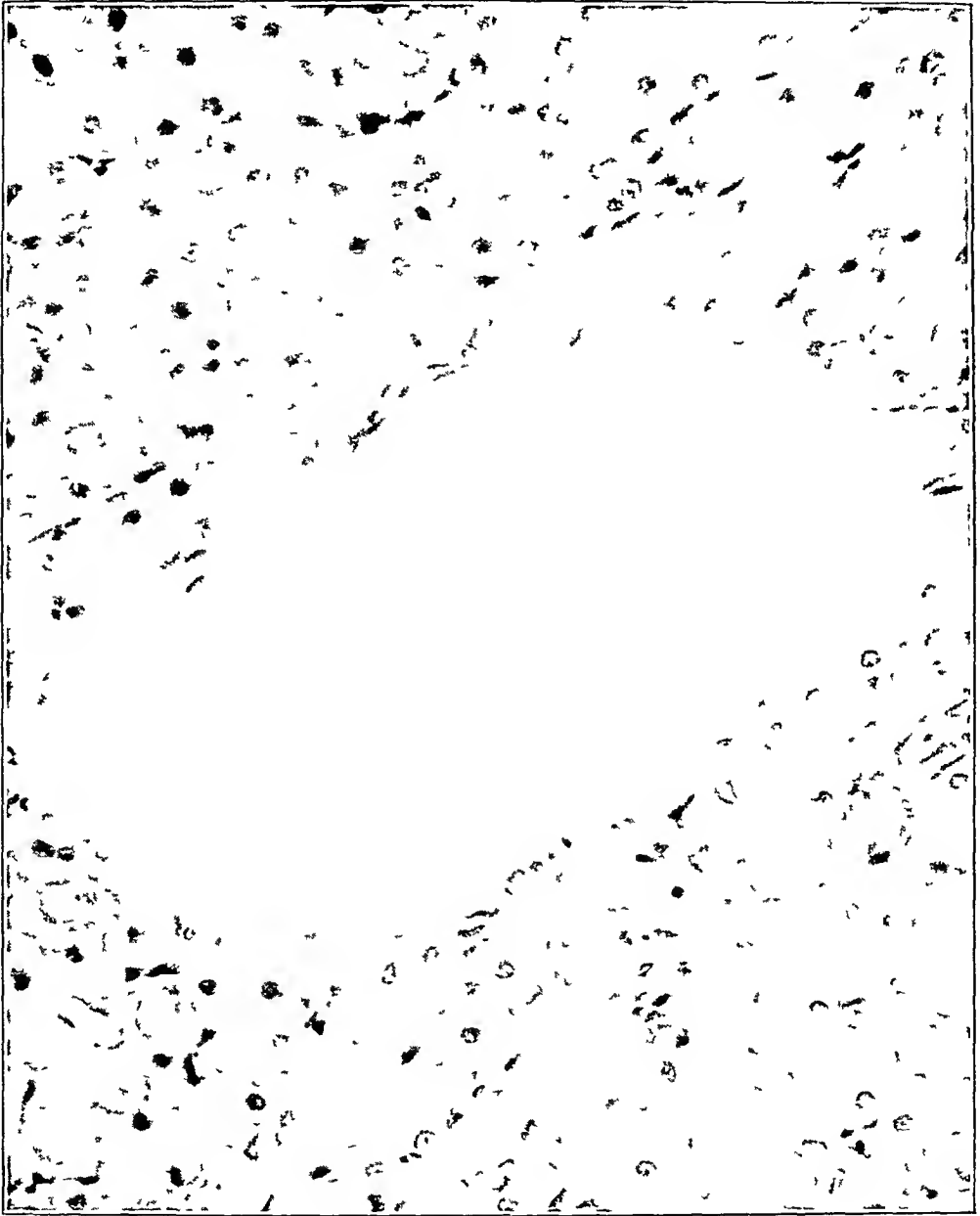


Fig 11—Section from the kidney of rabbit 3 which received repeated doses of 0.077 cc of novasurol per kilogram for twenty-three doses over a period of six months and was killed six weeks after the last dose. A small retention cyst is seen. Photomicrograph, 16 mm obj.

due to intestinal obstruction and partly to novasurol. In animals 12, 14 and 15, which succumbed at varying periods after repeated doses, there was little evidence of chronic damage, but varying amounts of acute degeneration were present in the kidney.

COMMENT

The foregoing pathologic changes correspond closely to those already described by Menten,²⁵ MacNider,²⁶ Kolmer and Lucke,²⁷ Schamberg, Kolmer and Raiziss,²⁸ Burmeister and McNally²⁹ and Elwyn³⁰ as being characteristic of the lesions produced by the various other mercuric compounds in common use.

The exact cause of the renal changes produced by novasurol is not clear. Various theories have been advanced, but there is no unanimity of opinion as to the method of action of mercury on the kidneys. Kaufman³¹ believed that mercury had a thromboplastic action producing thromboses, ischemia and subsequent degeneration. Later writers have been unable to substantiate this claim. Thromboses were not observed in this study. Moreover, it has been shown that even though hirudin has been added, thus preventing coagulation, similar damage occurred after poisoning with mercury. Kunkel³² advanced the idea that myocardial insufficiency was the factor responsible. This can hardly be accepted since such extreme changes are never seen even in cases of severe cardiac failure, and moreover, myocardial insufficiency is not observed except in the terminal stages. General vasomotor paralysis has been advanced as a cause by v. Mehring,³³ but low blood pressure does not necessarily accompany mercuric poisoning. Elbe³⁴ believes that

25 Menten, M. L. Pathological Lesions Produced in the Kidney by Small Doses of Mercuric Chloride, *J. M. Research* **43** 315, 1922.

26 MacNider, W. de B. A Study of the Acid-Base Equilibrium of the Blood in Acute Bichloride Intoxications, *Proc. Soc. Exper. Biol. & Med.* **14** 140, 1916-1917.

27 Kolmer, J. A., and Lucke, B. A Study of the Histologic Changes Produced Experimentally in Rabbits by Mercurial Compounds, *Arch. Dermat. & Syph.* **3** 531, 1921.

28 Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W. A Study of the Comparative Toxicity of the Various Preparations of Mercury with a Histological Study of Experimental Mercurial Nephritis, *J. Cutan. Dis.* **33** 819, 1915.

29 Burmeister, W. H., and McNally, W. D. Acute Mercury Poisoning. A Parallel Histological and Clinical Study of the Renal and Hepatic Tissue Changes as Compared with the Rapidity of Absorption and the Amount of Mercury Present in the Circulating Blood at the Time Such Changes Occur, *J. M. Research* **36** 87, 1917.

30 Elwyn, H. The Nephrosis of Mercury Poisoning or the Bichloride Kidney, Nephritis, New York, Macmillan Company, 1926, p. 227.

31 Kaufman, E. Neuer Beitrag zur Sublimatintoxication nebst Bemerkungen über die Sublimatniere, *Virchows Arch. f. path. Anat.* **117** 227, 1889.

32 Kunkel, cited by Weiler. *Virchows Arch. f. path. Anat.* **212** 200, 1913.

33 Von Mehring, J. Ueber die Wirkungen des Quecksilbers auf den thierischen Organismus, *Arch. f. exper. Path. u. Pharmacol.* **13** 86, 1880-1881.

34 Elbe. Die Nieren und Darmveränderungen bei der sublimatoergiftung des Kaninchens in ihrer Abhängigkeit von Gefassnervensystem, *Virchows Arch. f. path. Anat.* **18** 445, 1905.

mercury causes local constriction of the capillaries MacNider³⁵ claimed that the late changes in the kidney are due to an acid intoxication. Most writers, however, feel that the direct action of mercury on the epithelial cells is the real cause. The objection offered to this view is the low concentration in which mercury occurs in the blood. Flexner and Sweet,³⁶ however, have shown conclusively that this is the mode of

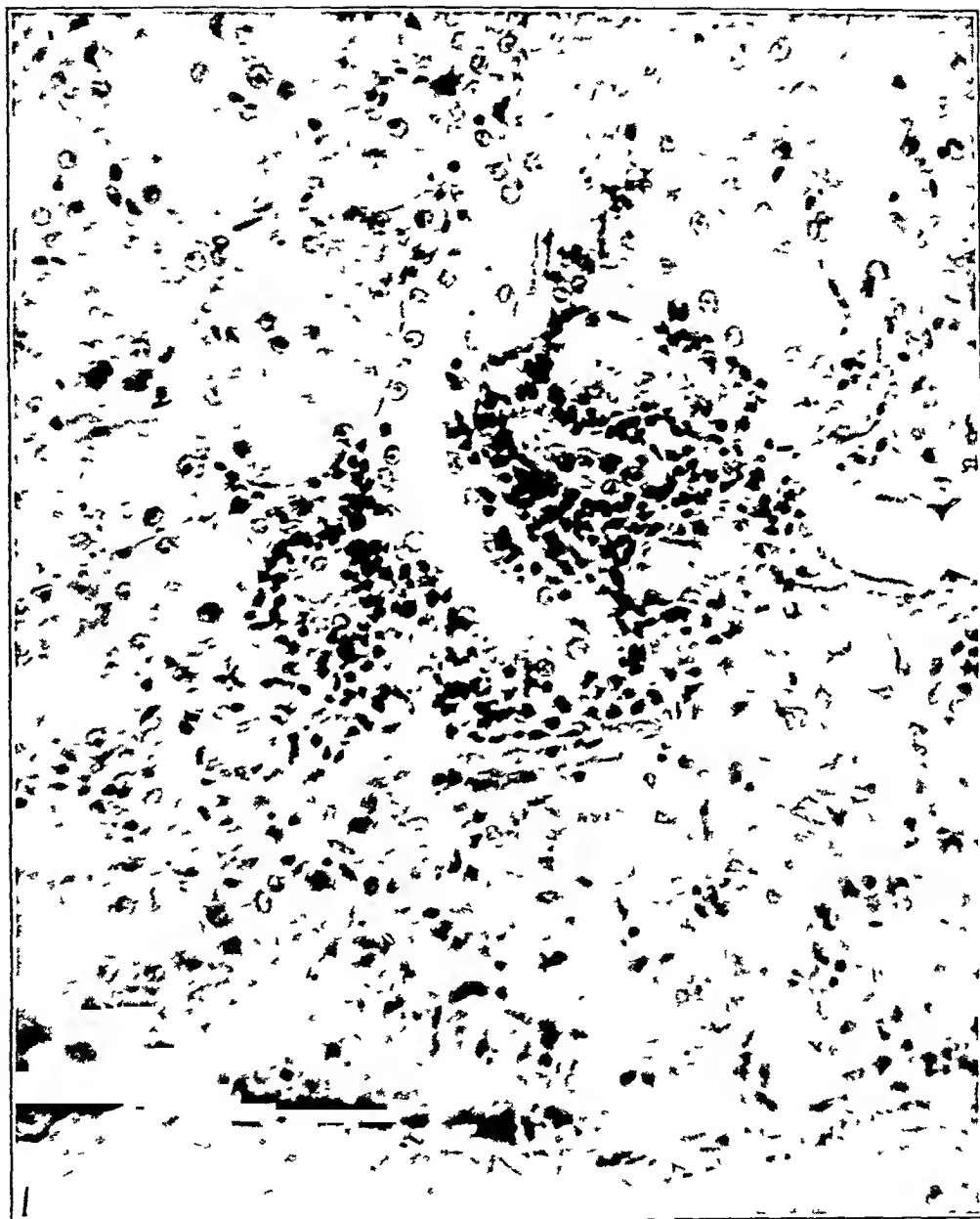


Fig 12—Section from the kidney of rabbit 2 which received repeated doses of 0.061 cc of novasurol per kilogram for twenty-three doses over a period of six months and was killed six weeks after the last dose. A small area of lymphocytic infiltration is shown. Photomicrograph, 16 mm obj.

35 MacNider, W. de B. A Study of Acute Mercuric Chloride Intoxication in the Dog with Reference to the Kidney Injury, *J. Exper. Med.* 27:519, 1918.

36 Flexner, S., and Sweet, J. E. The Pathogenesis of Experimental Colitis and the Relation of Colitis in Animals and Man, *J. Exper. Med.* 8:514, 1906.

action on the large bowel, and as mercury is also excreted by the kidney cells it seems reasonable to believe that mercury produces degeneration by directly poisoning the renal epithelium. The rapidity with which the changes take place also bespeaks a direct action. The fact that Huber ³⁷ has demonstrated that there are no arteriolae rectae



Fig 13—Section from the kidney of rabbit 2. This is a higher magnification of a portion of the area shown in figure 12. Photomicrograph, 4 mm obj.

in the kidney, but that all the blood passes first through the glomeruli before being distributed to the tubules, would also tend to rule out

³⁷ Huber, G. C. The Arteriolae Rectae of the Mammalian Kidney, *Am J Anat* 6:391, 1906-1907.

ischemia from any cause as a factor because we would then expect degeneration in the collecting tubules as well as in the convoluted tubules and in the ascending limb of Henle. It is therefore believed the novasurol causes degeneration in the kidney by directly poisoning the parenchymal renal cells.



Fig 14—Section from the kidney of rabbit 16 which received fifteen doses of 0.066 cc of novasurol per kilogram over a period of two months. This animal died from peritonitis following intestinal obstruction. The typical picture of a chronic nephritis is seen as evidenced by the thickening of Bowman's capsule, increase in interstitial connective tissue and replacement of the tubules. A small deposit of calcium is also present. Photomicrograph, 16 mm obj.

We have estimated the immediate lethal dose of novasurol as 0.7 cc per kilogram for the rabbit. Though in a general way this is an index of the toxicity of the drug, it is in no way a satisfactory guide as to its

possible poisonous properties when used therapeutically. Overwhelming doses administered intravenously kill the animal in an entirely different manner than do smaller doses acting over a period of time. MacNider³⁵ believed that when mercury is given by mouth, if death occurs within forty-eight hours it is due not to action on the kidney but rather to shock, which the poison induces through its corrosive action on the intestines and stomach. This cannot explain the death of rabbits 6 and 8 in this study as they died within three minutes after the drug was given. Jackson³⁷ has shown that large doses of mercury given intravenously to the dog cause the prompt appearance of great irregularity and finally fibrillation of the ventricles and death. If the vagus nerves were cut, death resulted from respiratory paralysis. It is probable that in rabbits 6 and 8, death resulted from one or other of the foregoing causes. Human beings and animals dying after about seven days, usually die in uremia.

Mercuric chloride theoretically contains about 74 per cent of pure mercury. Barbour³⁸ recorded the lethal intravenous dose for a rabbit as 4 mg per kilogram which would contain 3 mg of pure mercury. Kolmer and Lucke³⁷ and Schamberg, Kolmer and Raiziss,³⁴ stated that the toxicity of mercuric compounds varies closely with the amount of pure mercury the compound contains. The drugs used by them included mercuric chloride and the noncomplex organic compounds in common use. Novasurol contains approximately 34 per cent of pure mercury and is prepared as a 10 per cent solution. It was found that rabbit 4 receiving 0.168 cc per kilogram died in four days, whereas animals receiving 0.11 cc per kilogram regularly recovered. If the lethal dose is estimated as about 0.13 cc per kilogram, this would be equivalent to 4.42 mg of pure mercury per kilogram. Novasurol is thus estimated to be less toxic than mercuric chloride. Certain investigators maintain that inorganic mercurial salts in which mercury exists as an ion are organotropic and therefore more highly toxic than organic compounds. The explanation offered is that in inorganic mercurial salts the mercury ion being free combines with the proteins of the body, whereas in the organic compounds the element mercury is no longer free as an ion and hence does not attack proteins as vigorously. Such compounds are hence regarded as less toxic. This is the probable explanation for the difference between mercuric chloride and novasurol. Although Schamberg, Kolmer and Raiziss³⁴ did not find this difference between organic and inorganic compounds, the organic compounds used by them were relatively simple as compared with the highly complex novasurol.

38 Barbour, H. G. Mercuric Chloride Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, *J. A. M. A.* **64** 736 (Feb. 27) 1915.

Rabbit 17 was given a dose of 0.089 cc per kilogram and no damage was observed in twenty-four hours. If appreciable damage occurs, it is seen early, and hence such a dose did not damage the kidney. An equivalent dose for a man weighing 70 Kg would be about 6 cc. On the other hand, rabbit 28 received 0.098 cc per kilogram, and marked damage resulted. This would be equivalent to about 7 cc for a man weighing 70 Kg. The maximum single tolerated dose for the rabbit is apparently about 0.09 cc per kilogram, or, estimating it on the same basis for a man weighing 70 Kg, as about 6.5 cc. This would be equivalent to 3 mg of pure mercury per kilogram. Schamberg, Kolmer and Raiziss²⁸ have shown the single tolerated dose of mercuric chloride to be about 2 mg per kilogram. Though the single maximum tolerated dose of novasurol in the average rabbit is about 0.09 cc per kilogram, repeated doses of this magnitude and even considerably smaller doses repeated biweekly rapidly caused death. Thus, rabbit 12, with a dose of 0.09 cc per kilogram, died in one month after five doses. Rabbit 16, with a dose of 0.066 cc per kilogram, died in two months after fifteen doses, rabbit 15, with a dose of 0.053 cc per kilogram, died in three weeks after four doses and rabbit 14, with a dose as small as 0.038 cc per kilogram, which would be equivalent to only 2.66 cc for a man weighing 70 Kg, died in three weeks after five doses. It was felt that the last named animal was unusually susceptible to the drug. If these results can be used in estimating the toxicity of novasurol in man, one would consider that repeated intravenous doses of 3 cc for the average adult were too large and would be toxic especially for susceptible persons. MacNider³⁹ has shown that the kidney of nephropathic animals is susceptible to mercuric poisoning. Individual normal animals also have varying inherent resistances to mercury. This is probably also true for human beings and justifies the use of a small initial test dose and also the hesitancy most observers have in using novasurol in the presence of renal disease.

Of the three animals surviving repeated biweekly doses for a period of about six months, namely, rabbits 2, 3 and 13, 2 and 3 received an initial dose five weeks before the biweekly doses were begun. These two animals did not show any clinical evidence of poisoning at any time, even though they received 0.061 and 0.077 cc per kilogram per dose, respectively. Rabbit 13, on the other hand, did not receive such an initial dose, but biweekly doses of 0.041 cc per kilogram were given from the start. Though the dose injected was considerably smaller than that given to rabbits 2 or 3, in the first month during which time it received eight doses, this animal appeared ill and had diarrhea. It

³⁹ MacNider, W. de B. The Susceptibility of Naturally Nephropathic Animals to Acute Mercuric Chloride Intoxication, *J. M. Research* **39** 461, 1919

became weak and had difficulty in moving the hind limbs. During the second month, though the drug was continued, the animal recovered clinically and remained so until it was killed six months after beginning the injections. It would appear that rabbits 2 and 3 developed some tolerance to novasurol from the initial dose given five weeks before intensive treatment was begun.

Menten ⁴⁰ claimed that the damage to the kidney is more severe if mercuric chloride is given intravenously in high dilutions than when it is more concentrated. Thus, a toxic dose in 5 cc physiologic sodium chloride produced greater damage than a similar dose when given in from 0.5 to 0.1 cc. This factor was not investigated in this study, but may be the explanation for the increased diuresis obtained by Evans ⁵ when novasurol was given with from 20 to 30 cc of physiologic sodium chloride.

The pathologic picture produced by toxic doses of novasurol in this study was similar throughout, varying only in degree. Deposition of calcium in the rabbit is known to occur readily. Nakata ⁴⁰ claimed that calcification does not occur in the human before the fifth day. The earliest evidence in this study was seen in four days. Schmidt ⁴¹ claimed that the deposition of calcium does not occur unless there is injury to the colon thus interfering with the excretion of calcium, as from 90 to 95 per cent is excreted by this route.

SUMMARY

A study of the toxicity of novasurol was made by injecting it intravenously into the rabbit. Thirty-two animals were used. Doses of 0.7 cc per kilogram killed the animal within three minutes, and death was assumed to be due to fibrillation of the ventricles or to a direct action on the vital centers in the medulla. Doses of 0.168 cc per kilogram and over were lethal. If lethal doses were given but death was not immediate the length of life after treatment varied directly as the size of the dose. The severity of damage to the kidney varied directly as the size of the dose and as the length of time the rabbit lived after injection. The maximum single tolerated dose was estimated as about 0.09 cc per kilogram or about 3 mg of pure mercury. Repeated doses of 0.05 cc per kilogram were consistently toxic. This would be equivalent to a dose of 3.5 cc for a man weighing 70 Kg. In a number of instances, considerably smaller repeated doses produced death.

40 Nakata, J. Die Stadien der Sublimatmerc des Menschen nach ihren makroskopischen und mikroskopischen Besonderheiten, Beitr z pathl Anat u z allg Pathol **70** 282, 1922.

41 Schmidt, M. B. Ueber die Verkalkung der Nierenepithelien bei sublimatvergiftung und bei Dysenterie, Centralbl f allg Pathol u path Anat **30** 497, 1920.

In one animal, 0.038 cc per kilogram proved lethal in three weeks after five doses. Such a dose would be equivalent to 2.66 cc for a man weighing 70 Kg. Two rabbits given an initial dose that was fairly large and then given five weeks to recover were able to withstand repeated doses of 0.06 and 0.077 cc per kilogram, respectively, at from four to five day intervals for twenty-three doses without showing clinical evidence of toxicity and when killed the kidney showed but little change. Animals dying of repeated smaller doses after some weeks did not show the extensive damage to the kidney that was present in those dying early after a single lethal dose, although considerable degeneration was present. Single doses of 0.1 cc per kilogram and over showed damage to the kidney as early as one hour after injection, and the lesions became progressively more severe in direct proportion to the size of the dose and the time elapsed following the injection.

If pathologic lesions occurred in the kidney of a rabbit as the result of intravenous injection of novasurol, they were first seen in the proximal convoluted tubules. The earliest change consisted of swelling of the epithelium, loss of cell boundary, increased affinity for the acid stain and a gradual change in the nuclei from normal to pyknosis, karyorrhexis and complete disappearance. At first only irregularly scattered patches of such tubules were seen. These were largely subcapsular. If the dose had been small, degeneration did not proceed further, but as time went on and larger doses were given, degeneration became more extensive and more severe. Next in order the distal convoluted tubules and the ascending limbs of Henle showed similar early changes. At the same time, the degeneration in the proximal convoluted tubules became more marked. The cells became swollen to fill the lumen or desquamated, the nuclei disappeared and finally the tubule was represented by a structureless homogeneous, pinkish-staining necrotic mass. If the animal survived a lethal dose long enough, practically all the convoluted tubules, both proximal and distal, as well as the ascending limbs of Henle, underwent complete necrosis. By the fourth day evidence of regeneration in the form of young, irregular and occasionally multinucleated cells was present. The nuclei of these cells were large and vesicular, and in some instances, mitotic figures were present. In later stages, the tubules were lined by flattened epithelium. The earliest deposition of calcium was observed in four days and the largest amount in ten days. The glomeruli were normal except in the two animals already described. The collecting and connecting tubules, descending limb of Henle and the papillary ducts were not abnormal. In the early stages there was considerable hyperemia in the medulla, but this was never observed in the cortex. The vessels were unchanged. In the acute stages there was frequently edema of the interstitial tissue, and occasionally small nests of lymphocytic infiltration were seen.

In those animals surviving for longer periods evidence of slight chronic change was present in the form of small patches of lymphocytic infiltration, an increase in connective tissue and small retention cysts. It could not be definitely said that this chronic change was due to novasurol.

CONCLUSIONS

1 The toxicity of novasurol is somewhat less than that of mercuric chloride when based on the amount of pure mercury contained.

2 In the rabbit the toxicity of novasurol varies closely with the amount given per kilogram. It is suggested that when this drug is used therapeutically, the weight of the patient should be considered in estimating the size of the dose.

3 Repeated doses of novasurol equivalent to 3 cc. for a man weighing 70 Kg., when injected intravenously into the rabbit were toxic in certain animals. It is suggested that repeated doses for a man weighing 70 Kg. should not be larger than 2 cc. when given intravenously.

4 The tolerance of different rabbits for novasurol varies. The susceptibility of patients for the drug should be tested by an initial small dose of 0.5 cc. before intensive treatment is begun.

5 Certain rabbits given an initial dose and then allowed to rest for a few weeks withstood repeated large doses over a long period of time. It was felt that the initial dose increased the tolerance of such animals.

6 The pathologic lesions produced in the kidney of the rabbit by toxic doses of novasurol are identical with the lesions already described as produced by the various other mercuric compounds in common use.

DIABETES

A STATISTICAL STUDY OF TWO THOUSAND CASES *

HENRY J. JOHN, M.D.

CLEVELAND

The statistical study of 1,000 cases of diabetes¹ which I reported a year ago was an attempt to correlate my data with those of other authors and to offer evidence of the different factors involved in the study of this disease. The present statistical study in a larger series is but a continuation of my previous presentation.

During the period which this study covers, March 1, 1921, to Nov. 1, 1927, the total number of new patients admitted to the clinic was 87,449. Thus the incidence of diabetes among our patients during this period was 2.28 per cent, while in the first series, among the 55,939 patients seen in the clinic during the period covered by that series March 1, 1921, to Aug. 31, 1925, the diabetic incidence was 1.8 per cent.

AGE AND SEX INCIDENCE

The distribution of these cases in each series according to sex and to the different age decades is shown in chart 1 and also in table 1, while table 2 correlates my own data with those of other authors. On the whole, in these respects, the second series closely resembled the first. The numbers of cases in males and in females in each decade are practically equal. Although the incidence of diabetes is highest in the fourth decade in this series, the fifth, sixth and seventh decades furnished most of the cases. As obesity, also, begins to manifest itself in the fourth decade, and usually persists, one is forced to wonder how much relation it bears to diabetes. Young people are usually too active to acquire an abundance of adipose tissue, but infection, on the other hand, predominates in the first two decades. As the incidence of diabetes is comparatively low in the earlier age decades, it would appear that the predominance of infection as an etiologic factor in the production of diabetes must be doubted, though that it at least occasionally is a predisposing factor cannot be denied.

In a more detailed analysis of the incidence of diabetes in the first three decades, among the 199 cases included, 32 occurred in the first decade, 54 in the second, and 113 in the third. In the second series in this group the female incidence predominates over the male by 36.9

* From the Cleveland Clinic.

¹ John, H. J. Diabetes. A Statistical Study of One Thousand Cases, *Arch. Int. Med.* **39**: 67 (Jan.) 1927.

per cent, whereas in the first series the numbers of male and of female patients were practically equal. This may be but a possible coincidence, however.

The rôle played by heredity in the production of diabetes is mentioned by all authors. A compilation of the observations of various authors on this subject, and also of my own is given in table 3. The figures in the second series again almost duplicate those in the first series, i.e., 10 per cent in the second series as compared with 9.7 per cent

TABLE 1—*Classification of Two Thousand Cases of Diabetes According to Age and Sex Incidence**

Age Decade	First Series		Second Series		Total Series		Grand Total	Incidence Per Cent
	Male	Female	Male	Female	Male	Female		
1	11	7	6	8	17	15	32	1.60
2	15	12	14	12	29	24	53	2.65
3	22	24	27	42	49	66	115	5.75
4	56	56	65	65	121	121	242	12.10
5	98	128	106	131	204	259	463	23.15
6	125	111	123	161	248	275	523	27.65
7	131	156	128	110	259	266	525	26.40
						141	141	
Total	459	527	469	531	928	1,058	2,000	

* In this table and in tables 5, 6, 7, 8, 9, 10 and 12 the data were compiled from the author's study of 2,000 cases of diabetes.

† Unclassified.

TABLE 2—*Incidence of Diabetes According to Age Decades Compiled from Literature**

	Age Decades							
	1	2	3	4	5	6	7	8
Frerichs	1	7	10	18	25	25	11	1
Seegen	0.1	1	16	16	24	0	10	0.5
Grube		17	28	11.2	23.1	39.5	18.1	3.4
Schmidt	0.85	11	9.1	17.3	22.5	26	10	3.3
Pavy	0.58	11.9	7.13	16.4	21.9	0.7	13.4	2.5
Kulz	1	5	4.6	17.2	6	25.8	9.2	0.1
Von Noorden		9.4	2.1	10	21	17.7	1	0.44
Von Noorden	1.17	2.41	6	9.57	12.6	14	2.1	1
John (2,000 cases)	1.6	2.65	5.75	12.1	23.15	37.65	26.4	

* After Joslin (*The Treatment of Diabetes Mellitus*, Philadelphia, Lee & Febiger, 1916 p. 128).

† Light cases.

‡ Severe and moderately severe.

in the first. The incidence of the heredity factor in my series is much lower than that given by Joslin, von Noorden and others, yet I have closely questioned each patient. I can see no explanation for this variation, as only Grube and Frerichs give figures similar to mine. The heredity factor has been discussed in a previous publication.¹

BLOOD SUGAR CONTENT AND GLYCOSURIA

The blood sugar of the patients on admission varied from below 120 to above 900 mg. per hundred cubic centimeters. The low blood sugar values may be accounted for by the fact that an estimation of

blood sugar is always made immediately after a patient is admitted to the hospital, and in some cases insulin had been administered shortly before that time. Patients whose diabetes is properly controlled will also present a normal fasting blood sugar on admission. These points must be borne in mind in the study of these figures. Data on the blood sugar in all cases were summarized in even amounts, varying by 50 or 100 mg per hundred cubic centimeters. This showed that in the largest number of cases in both series the blood sugar varied between

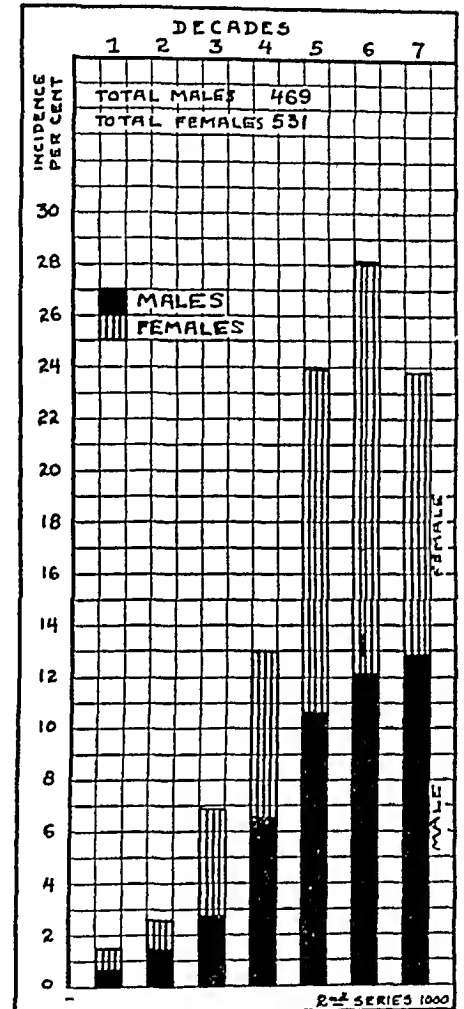
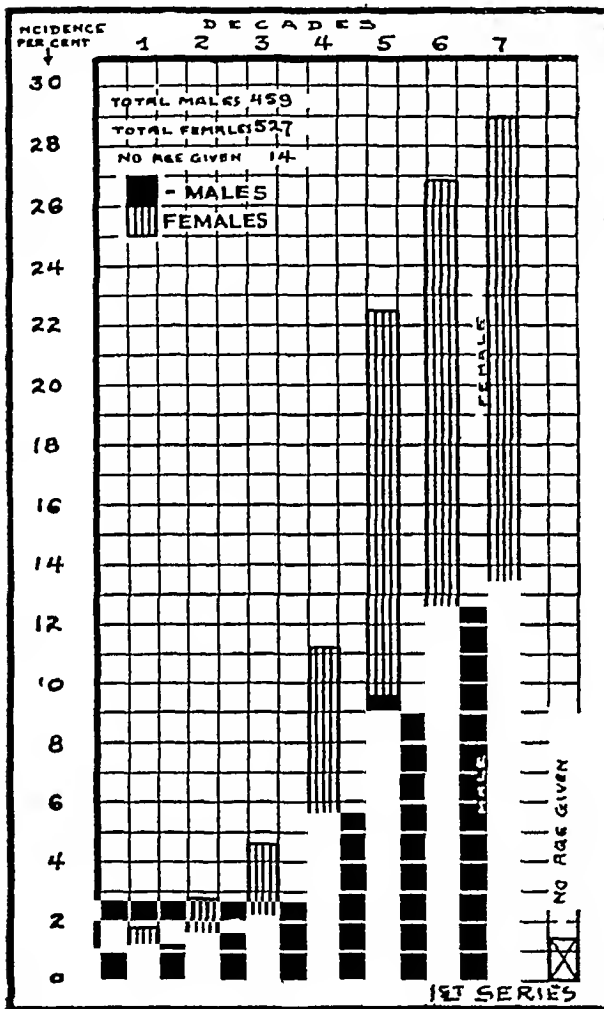


Chart 1—The sex and age incidence of diabetes (From the author's series of 2,000 cases of diabetes)

150 and 250 mg per hundred cubic centimeters, the number remained high, however, up to 300 mg, above which figure the number of cases at higher levels began to diminish. In seventy-six cases, however, the blood sugar was 500 mg per hundred cubic centimeters or more.

Observations were made on the presence or absence of glycosuria on admission together with estimations of blood sugar, the former being of especial interest in that they showed 159 cases in which glycosuria was present although the blood sugar content was below 180 mg. Above that

level one naturally expects to find glycosuria, but in twenty-six cases in which the blood sugar was 120 mg per hundred cubic centimeters glycosuria was present. The point which one must derive from these data is that the blood sugar level does not by any means disclose the level of renal threshold. The urine collected at the moment when the blood is taken for sugar estimation is not the urine which has been secreted during those particular few minutes, but rather includes that urine plus all the urine which was secreted during the period of time since the last preceding voiding. It is necessary, therefore, to determine what the blood sugar level was throughout that period. Did it reach a high level above that of the renal threshold, and gradually drop to the level at the time the specimen was taken, or was it at the same level at which it was found throughout the period since the last preceding

TABLE 3—*The Hereditary Factor in the Incidence of Diabetes*

Author	Date of Compilation	Number of Cases	Percentage of Cases with Hereditary or Familial History of Diabetes	
Grube			8.0	
Frerichs		400	9.8	
Seegen			14.0	
Schmitz			20.0	
Kulz		692	21.6	
* Williamson		500	22.0	
Bouchard			25.0	
Naunyn	1905	398	17.0	
Von Noorden	1917		25.4	
Joslin	1923	2,800	21.0	Hereditary 18.5
				Familial 6.9
John	1927	1,000	9.7	Hereditary 15.0
				Familial 7.0
John	1928	1,000	10.0	Hereditary 4.6
				Familial 5.1
				Hereditary 6.1
				Familial 3.9

* After Joslin (The Treatment of Diabetes Mellitus, Philadelphia Lea & Febiger, 1916 p. 126)

voiding? These figures per se do not give definite information as to the patient's renal threshold, this must be determined in each case if specific information on that particular point is desired. It is interesting however, to observe that in a good many definitely diabetic patients in whom the blood sugar content is low glycosuria is present.²

In blood sugar values in diabetic patients who do not show glycosuria the high blood sugar values are interesting for they show how relatively impermeable the renal filter is to dextrose. These figures too have a more definite value than those given for patients who showed glycosuria, because it is known that during the period from the last preceding voiding the blood sugar content was not only as high as the estimated value here given, but that in some cases, no doubt it was much higher. The highest value of blood sugar without the coexistence of glycosuria was 390 mg per hundred cubic centimeters. The same data given separately in each series are represented graphically in chart 2.

² John, H. J. J. Lab & Clin Med 9 626, 1923-1924

THE ROUTINE TREATMENT AND PROGRESS OF DIABETIC PATIENTS

The improvement of diabetic patients today is infinitely greater than it was before the insulin era. The patients are better nourished and are able to work and carry on as only those with the lighter forms of the disease were able to do in the preinsulin period. Many patients get

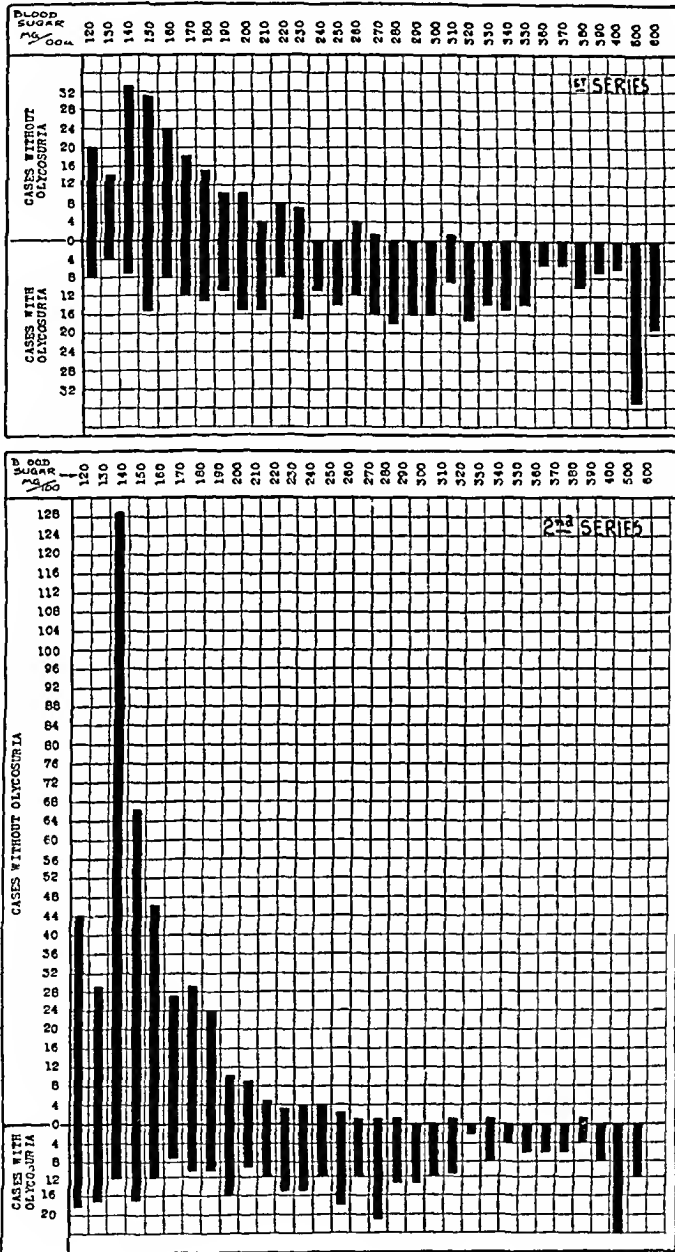


Chart 2—The incidence of glycosuria as compared with the absence of glycosuria at different blood sugar levels (From author's series of 2,000 cases of diabetes)

along well without insulin, especially the older ones, as in the case of a woman, aged 58, data of whose case from July 22, 1924, to Dec 6, 1927, are given in table 4. Even since a period of two weeks in the hospital, during which insulin was administered for twelve days, she had been

able to go without insulin. A similar history is that of a man, aged 46, who received insulin for only eight days. His blood sugar on admission was 319 mg per hundred cubic centimeters. His continued progress to the present date without insulin is shown in chart 3. Similar data can be given from a large number of cases. Diabetes in the old

TABLE 4—*Lasting Effects of Insulin in the Treatment of Diabetes as Indicated by Blood Sugar Determinations for a Prolonged Period After Its Discontinuance in the Case of a Woman, Aged 58*

Date	Blood Sugar Mg. per 100 Cc	Insulin		
		8 A M	12 M	5 P M
1921				
7-22	384			
7-27	196	10		
7-28	241	0		10
7-29	222	20	10	10
7-30	206	20	10	10
7-31	102	20	10	10
8- 1	200	20	10	10
8- 2	158	12		10
8- 3		20		10
8- 4	148	20		
8- 5	171	20		
8- 6	155	20		
8- 7	117	20		
8- 8	111			
8- 9	118			
8-12	151			
8-23	131			
9- 6	120	Date	Blood Sugar Mg. per 100 Cc	
9-17	125			
9-30	131			
10-14	123			
10-28	108	1926		
11-12	130	1-26		116
11-29	101	2- 6		89
12-20	113	3-10		80
		5-26		113
		6-17		88
1- 9	115	7- 7		125
2- 4	128	7-27		66
3- 4	117	9- 1		95
7-20	110	9-24		108
1- 6	110	10-20		116
4-27	108	11- 4		132
6- 1	116	12-11		109
6-25	113		1927	
7-10	117	1-11		126
7-21	113	2- 2		123
8- 3	79	3- 7		128
8-18	87	3-24		117
9- 9	111	4-20		111
9-29	100	5- 1		130
10-15	90	6- 1		139
11-18	97	6-20		132
12- 8	118	7-22		126
		8-30		101
		10-10		132
		12-6		139

is usually mild unless rendered severe by failure to adhere to the prescribed regimen.

It is my practice to administer insulin to every patient when he first comes to the hospital for the reason that thus the stay in the hospital may be shortened. In the treatment of persons with diabetes there are four chief objectives: (1) to get the patient as nearly normal as possible, (2) to find out what is required to gain and maintain the normal state,

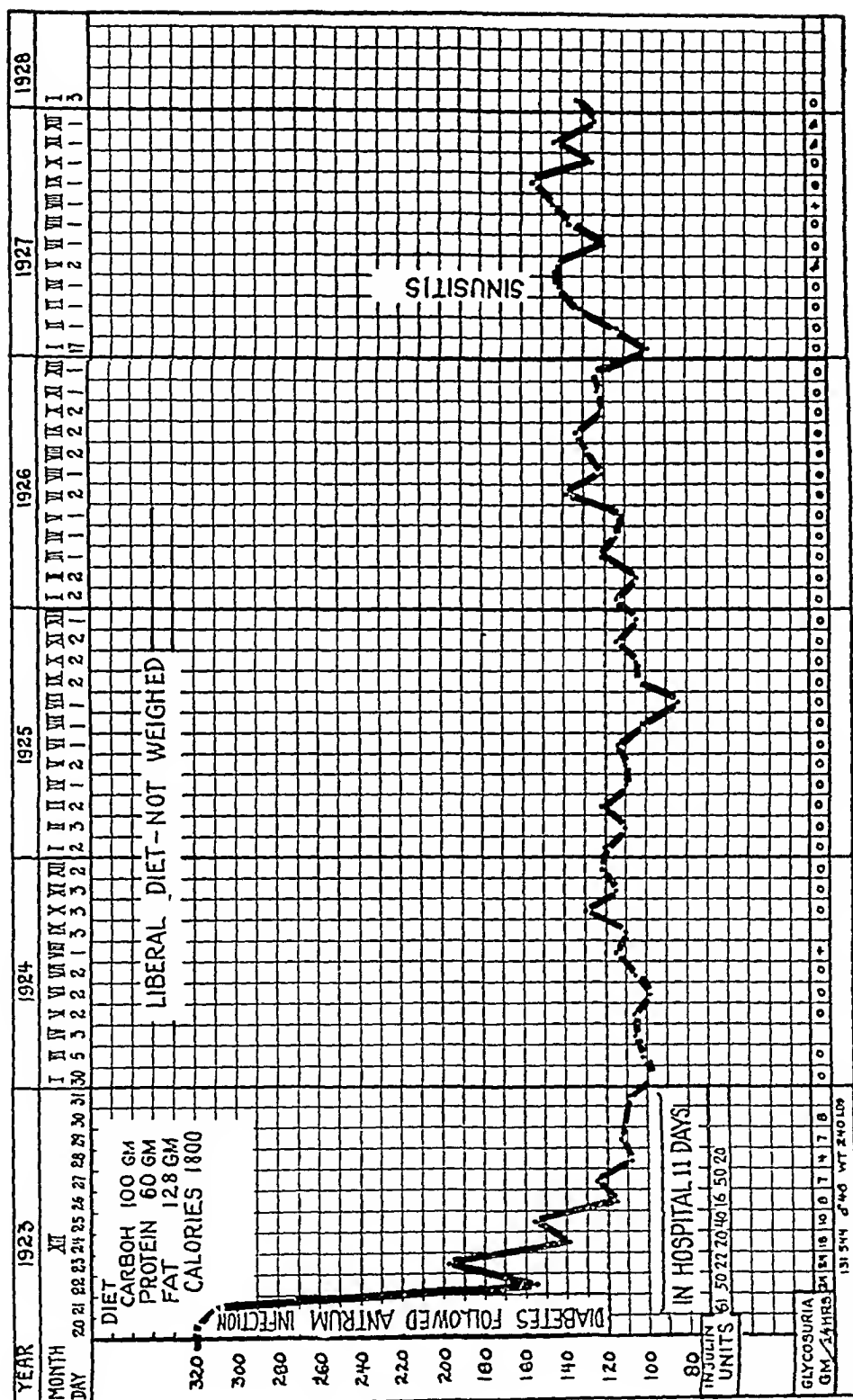


Chart 3—Lasting effects of insulin in the treatment of patients with diabetes as indicated by blood sugar determinations over a prolonged period in the case of a diabetic patient, aged 46 years

(3) to plan a livable—not a starvation—diet so that the patient may hold his job, and (4) to instruct the patient in the routine he must follow if he is to maintain the best possible status

To attain the first objective one can simply starve the patient, thereby weakening him still more but eventually reducing his blood sugar to the normal level, or one can place a patient on a livable diet from the start and use enough insulin to bring his blood sugar to the normal level more

TABLE 5—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance**

Age of Patient, Years	Duration of Diabetes, Months	Duration of Insulin Treatment, Days	Period Since Discontinuance of Insulin, Months	Blood Sugar Content when Insulin was Started Mg. per 100 Cc	Present Blood Sugar Content Mg. per 100 Cc
4	6	5	5	375	78
18	12	77	9	255	72
31	42	11	42	241	105
35	24	210	10	190	122
40	30	7	9	228	127
44	54	8	20	311	125
46	6	115	5	228	89
47	72	180	9	23	169
48	24	42	24	272	110
49	42	8	18	349	123
50	24	6	24	277	122
50	84	30	0	480	110
51	24	20	12	275	155
51	27	10	27	38	105
52	42	2	42	176	15
53	42	10	14	255	153
55	56	6	5	224	144
57	12	13	6	240	123
57	72	4	18	222	153
58	42	12	42	24	156
58	84	2	48	179	97
60	12	13	12	250	84
61	6		24	270	145
62	132	11	60	19	129
63	30	9	9	44	128
64	10	5	42	261	85
64	18	4	15	162	14
65	60	10	54	27	109
66	18	33	42	222	138
66	42	10	42	278	116
66	42	9	42	241	119
67	72	2	72	242	132
68	108	300	42	57	127
68	56	3	6	238	86
69	48	11	12	400	115
73	24	45	16	276	106
76	12	9	12	428	107

* Arranged in order of ages of patients

or less rapidly, as is desired. From the economic point of view, certainly, the second procedure is the logical one. To accomplish this purpose, one must juggle not the diet but the insulin until one finds the dosage which will maintain an approximately normal blood sugar content with a livable diet. The rationale of this procedure is clear for no matter how much a limited diet may apparently accomplish as far as the control of the blood sugar is concerned, it has failed hopelessly if the patient is discharged on a diet which is insufficient to maintain his weight and energy. Such was the general practice before the insulin era when all the physician had to work with was the endogenous

insulin still available in the patient's body, and when raising the diet above what that limited amount of insulin could care for meant disaster. The emaciated, weak, discouraged diabetic person whose agony was only prolonged by such measures is today but a pitiful memory.

I do not mean to advocate the use of an unlimited amount of insulin—that would not be rational—but I mean that one should employ the smallest amount of insulin which is required to accomplish the desired

TABLE 6—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance **

Duration of Diabetes, Months	Age of Patient, Years	Duration of Insulin Treatment, Days	Period Since Discontinuance of Insulin, Months	Blood Sugar Content when Insulin was Started, Mg per 100 Cc	Present Blood Sugar Content, Mg per 100 Cc
6	4	5	5	75	78
12	18	75	9	265	72
12	57	13	6	340	123
12	69	12	12	250	84
12	76	9	12	425	107
24	25	210	10	190	122
24	48	42	24	272	110
24	50	6	24	277	122
24	51	99	12	275	129
24	73	45	18	236	103
27	51	10	27	206	105
30	63	9	30	344	128
30	40	7	30	228	127
36	46	135	36	238	89
36	55	6	36	234	143
36	61	'	24	230	145
36	68	3	36	238	86
40	61	5	42	261	85
42	38	12	42	384	120
42	53	10	13	225	122
42	52	2	42	176	122
42	49	8	48	219	122
42	1	11	42	241	105
42	66	19	42	258	116
42	66	9	42	241	119
48	69	11	12	400	111
48	66	33	42	222	128
48	64	1	45	182	124
54	44	8	30	313	125
60	65	10	54	223	109
72	67	2	72	222	122
72	57	4	48	262	123
72	47	480	30	323	100
84	59	20	30	409	110
84	58	2	48	179	99
108	68	309	42	271	127
122	62	11	66	319	126

* Arranged in order of duration of diabetes

result in each case. It must be borne in mind that insulin loses its effect when the dosage is increased, i.e., 2 units of insulin produces relatively a greater effect than 20 units.

That a patient who is taking insulin needs to continue its use always is a fallacy. In tables 5, 6 and 7, I have compiled data in regard to a series of cases of diabetes in which insulin was used continuously for varying lengths of time (from 2 to 480 days). In these cases in which the patients, who ranged in age from 4 to 76 years, have discontinued the use of insulin for from five to seventy-two months, the blood sugar content either has remained within normal limits or has shown but a

slight rise. When the points that I have already explained are made clear to the patients who have this fear of the treatment with insulin, they immediately see the rationale of the whole procedure. It is not fair for the patient who places himself in the physician's care to dictate his own terms of treatment, and the physician's problem is to satisfy him by showing him the facts in the proper light.

TABLE 7—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance**

Period Since Discontinuance of Insulin, Months	Blood Sugar Content when Insulin was Started, Mg per 100 Cc	Present Blood Sugar Content, Mg per 100 Cc	Age of Patient, Years	Duration of Diabetes, Months	Duration of Insulin Treatment, Days
5	375	78	4	6	5
6	340	123	57	12	13
9	265	72	18	12	75
10	190	122	35	21	210
12	250	84	60	12	15
12	428	107	76	12	9
12	275	139	51	24	90
12	100	110	49	18	11
13	335	133	53	42	10
18	236	106	73	24	45
24	270	145	61	6	3
24	277	122	50	24	6
24	272	110	18	24	42
27	306	105	51	27	10
30	144	128	63	30	9
30	228	127	40	30	7
30	313	125	11	54	8
30	323	160	47	72	450
30	100	110	50	84	30
36	208	86	68	40	5
36	231	111	55	40	6
36	238	89	16	6	15
42	261	85	64	40	5
42	384	170	58	12	12
42	176	130	52	12	2
42	211	100	31	42	11
42	258	116	60	42	10
42	241	119	66	42	9
42	222	138	66	48	33
42	373	127	68	108	360
45	182	144	64	18	4
48	292	146	57	72	4
48	179	90	38	84	2
48	319	124	40	42	8
54	333	109	65	60	10
66	319	126	62	152	11
72	232	122	67	72	2

* Arranged in order of periods since discontinuance of insulin.

COMA

The total number of patients with diabetic coma in this series was eighty-five, an incidence of 4.25 per cent. Of these I myself treated fifty-nine, while twenty-six were treated in other cities. The statistics of this group of cases may be summarized in table 8. The data are given in detail in tables 9 and 10.

The deaths elsewhere are to be regretted. Often they were wholly unnecessary, because either the patient absolutely disregarded the prescribed routine or he or his relatives misunderstood the essential factors in the treatment. The unfortunate idea that a patient who is not eating

TABLE 8—Data of Patients with Diabetic Coma

Total number of diabetic patients	2,661
Total incidence of coma	65 (4.25%)
Died elsewhere	26
Number of patients with diabetic coma treated by the author	59
Living	48 (81.35 per cent)
Dead	11 (18.65 per cent)

TABLE 9—Examinations of Blood of Patients in Coma on Admission*

No of Case	Age of Patient	Sex †	Living					Previous Duration of Diabetes
			Blood Sugar Mg per 100 Cc	Plasma Acetone	Lipemia	Plasma Carbon Dioxide		
3	1	♂	428				1 year	
1	15	♂	310	trace		32.6	1 month	
2	2	♂	476			13.7	6 months	
4	4	♂	375				2 years	
5	4	♂	440	+++	++		1 year	
6	8	♂	460			15.7	5 years	
7	9	♂	440	++		20.2	6 years	
8	10	♂	666	++	+			
9	14	♂	441				2 months	
10	15	♂	447	++	++++	24	3 months	
11	16	♂	363	+++	++++	23.3	3 months	
12	18	♂	410	+++		27.1	2 months	
13	20	♂	405	+++	++++		2 years	
14	21	♂					6 months	
15	22	♂	652	+++		11.8	4 years	
16	22	♂	320	++		37	4 years	
17	23	♂	467	+++			5 years	
18	24	♂	360				2 years	
19	25	♂	460	+++		16	1½ years	
20	26	♂	400	+++		21.4	1 year	
21	26	♂	454	+		21.4	2 years	
22	26	♂	544	+++		27.1	2 years	
23	28	♂	696	++	+		4 months	
24	30	♂	467	++	0	27.1	8 years	
25	31	♂	344	+++		30	10 years	
26	31	♂	376	trace	+	19.5	2 years	
27	31	♂	788	+		15.7	1 year	
28	34	♂	460	+++		20.9	4 years	
29	34	♂	167	++		16.6	4 years	
30	35	♂	200	+		46.4	1 year	
31	37	♂	638	+++	+++	11.8	7 years	
32	38	♂	626	+++			2 months	
33	44	♂	447				2 years	
34	45	♂	600	+			1½ years	
35	48	♂	408	+		19.2	6 months	
36	48	♂	434	—		44.3	6 months	
37	50	♂	626	+		30.9	2 years	
38	50	♂	810	+			1 year	
39	50	♂	1664	+			1 year	
40	54	♂	333	++		21.4	3 years	
41	56	♂	389	+++		29	2 years	
42	59	♂	563	0	—		13 days	
43	59	♂	679	++			2 years	
44	61	♂	880	+++		25.2	8 years	
45	63	♂	353	+++		37.6	2 years	
46	64	♂	200				11 years	
47	67	♂	525	+++		13.7	6 years	
48	67	♂	516	++	0	17.6		
Dead								
49	11	♂	300			25.2	20 days (Before insulin era)	
50	17	♀	652	++		17.6	1 day (Died 1 hr after admission)	
51	18	♀	447	++			6 months (Before insulin era)	
52	27	♀	778			21.4	3 years (Pneumonia)	
53	41	♀	810	++		9.9	6 years (Cardiac failure)	
54	50	♀	516	+++		23.2	1 year (Pneumonia)	
55	55	♂	516	++		10.7	2 years (Gangrene, uremia)	
56	56	♀	389	---		29	2 years (Gangrene, septicemia)	
57	58	♀	880	---		11.8	13 years (In coma nine hours before seen)	
58	59	♀	318	0	0		13 days (Septicemia)	
59	62	♂	467	—				

* Arranged in order of ages of patients.

† In this column ♂ designates male, and ♀, female.

must not take insulin still seems to be in vogue. When a patient is unable to take or to retain food and starts vomiting, it seems logical to the family to withhold insulin for fear of hypoglycemia, and naturally acidosis increases while the patient gradually but definitely drifts into coma. Such a state may be initiated by tonsillitis or some other infection. The physician must impress on the patient the fact that whether or not one eats, the body keeps on burning calories just the same with

TABLE 10—Examinations of Blood of Patients in Coma Who Died Elsewhere*

No. of Case	Age of Patient	Sex †	Blood Sugar Mg per 100 Cc	Plasma Acetone	Lipemia	Plasma Carbon Dioxide	Duration of Di- betes	Comment
1	7	♂	326	+	+		10 days	Died at home
2	9	♂					5 years	Refused treatment
3	10	♂					20 days	Died at home, teeth extracted coma followed
4	12	♂					9 months	Broke diet at home
5	13	♂					1 year	Died at home
6	14	♂					1 year	Broke diet continuously
7	14	♂					10 days	Died in coma in another hos- pital
8	19	♂					13 days	Died at another city
9	21	♀	236				3 years	Died at another hospital follow- ing abortion
10	22	♂	497	+			3 months	Died at home
11	28	♂					6 months	Died at home, broke diet
12	40	♂					1 year	Died at home, broke diet
13	10	♂					2½ years	Died at home, no treatment
14	14	♂					8 months	Died at home, hyperthyroidism
15	16	♂					1 year	Died at home
16	48	♂	535	+++		12.6	1 year	Died at another hospital
17	48	♂	333	0			8 years	Died at another hospital
18	50	♂					5 years	Died at home, tuberculosis syphilis
19	50	♂	151				2 years	Died at home
20	51	♂					2 years	Died at home follow up infection on finger
21	58	♂	467	+++			9 years	Died at another hospital
22	59	♂					5 years	Died at home
23	60	♂	768				2 months	Died at home
24	61	♂	500	+		59.5	7 years	
25	62	♂	497	0			2 years	Died at home, also pulmonary tuberculosis
26	68	♂						Died at home

* Arranged in order of ages of patients.

† In this column ♂ designates male and ♀, female.

only this difference—when food is taken these calories are supplied from without, whereas when food is not taken these calories are supplied by the burning of one's own tissues. It follows that in either case insulin is needed to accomplish this burning. The patient usually grasps such an explanation quickly and then begins to realize the rationale for uninterrupted insulin therapy. As a matter of fact if a patient starts vomiting he needs more insulin. If one perceives the odor of acetone on the patient's breath and if heavy acetonemia or acetonuria is present, the quickest way to overcome the acidosis which is indicated by these signs is by the intravenous administration of 500 cc. of a 10 per cent solution

of dextrose, with from 30 to 40 units of insulin and $\frac{1}{4}$ grain (16 mg) of morphine sulphate. This treatment should follow a gastric lavage. The lavage is continued until the returned fluid is clear, when from 500 to 1,000 cc of the solution is left in the stomach. Following these procedures the patient practically always has a few hours of quiet sleep, and awakens refreshed and changed for the better.

On the other hand, when some irrational therapy is adopted in place of these measures, what happens? The vomiting becomes more and more intense, and the state of dehydration is increased with a resultant increase in the degree of acidosis. As the result of the increased acidosis more vomiting occurs, and so a vicious circle is established which must be broken up if the patient is to get well.

Much has been written on the routine treatment of persons in coma. Joslin's³ routine is well established and hardly needs emphasis. There are three points, however, that I wish to stress: (1) the administration of a sufficient amount of insulin to produce the desired effect of clearing up acidosis and lowering the blood sugar level, this may take anywhere from 80 to 700 units per twenty-four hours, (2) the use of 10 per cent dextrose intravenously, and (3) hospitalization of the patient.

There is a difference of opinion regarding the administration of dextrose when the blood sugar is already at a high level. Why add more dextrose and raise the blood sugar still more? It was true in the pre-insulin era that dextrose should not be administered to patients in whom a high degree of hyperglycemia and acetonemia were present, because there was not sufficient insulin available in the body for the storage and metabolism of the added sugar. At that time the intravenous administration of physiologic sodium chloride solution was a more rational measure. Now, however, one can use insulin in sufficient quantity to metabolize almost any amount of dextrose.

Suppose that in such a patient the blood sugar content is 600 mg per hundred cubic centimeters. This makes the total circulating blood sugar 600 times 50 (considering 5,000 cc as the total amount of circulating blood), which equals 30,000 mg or 30 Gm. If 500 cc of a 10 per cent dextrose solution is given, 50 Gm of dextrose will have been added, and there will be a total of 80 Gm in the blood stream. From this should be deducted 120 mg by 50 (the normal blood sugar content) or 6 Gm, 80 Gm minus 6 Gm equals 74 Gm, the surplus amount of sugar in the blood stream. Theoretically, one unit of insulin is supposed to burn up 2 Gm of dextrose, therefore, to consume 74 Gm of sugar, 37 units of insulin will be required. Therefore, when 500 cc of a 10 per cent solution of dextrose is administered at least 40 units of insulin is given without producing hypoglycemia. In an hour, 20 units more

³ Joslin, E. P. *The Treatment of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1916, p. 128.

is given, and this dosage is repeated perhaps for several hours. The patient appears to absorb these large amounts of insulin like a sponge.

It is an easy matter to differentiate diabetic coma from an insulin reaction—simply examine the urine for glycosuria. If the urine is loaded with sugar, then the condition is coma. If the urine is sugar free, then in the presence of a history of insulin therapy the condition is probably a hypoglycemic reaction. This procedure takes only a few moments, and a special apparatus is not required. If this test is applied promptly, valuable time need not be lost or the patient's chances of recovery jeopardized.

Is a more marked hyperglycemia produced by the use of dextrose? For a short time immediately following its administration, hyperglycemia is produced—that is to be expected just as a postprandial hyperglycemia is produced in a diabetic or even in a normal person—but this quickly subsides, and if the blood sugar is examined hourly, one rarely finds a slight rise but rather a fall in 95 per cent of the cases.

A year ago I published the data concerning blood sugar readings¹ which were made at varying intervals just before and just after the administration of dextrose and insulin. From those figures it is clear that the added sugar is burned up in the body. Incidentally, the acetone bodies are burned up with it, as is shown by the disappearance of acetonemia and acetonuria and by the rise of the respiratory quotient. Liquids are incidentally supplied to the dehydrated body by this painless method, which is much preferable to hypodermoclysis, although the latter method is to be used whenever it is indicated or is more expedient.

The actual amount of insulin which is needed in any given case varies considerably and can be estimated best by following the blood sugar fluctuations (blood sugar readings can be made at half hour intervals), and also by estimating the decreased glycosuria, in which case the patient may have to be catheterized. In chart 10 is shown the routine followed in a case of coma in a little girl, aged 2 years, who was brought to the clinic with a blood sugar content of 476 mg per hundred cubic centimeters. Her plasma carbon dioxide content two and a half hours after two doses of insulin had been administered was still 13.6. Between 7 a. m. and 4 p. m., she received 125 units of insulin in 16 doses, and by 4:30 p. m. her blood sugar was 80 mg per hundred cubic centimeters. The plasma carbon dioxide rose toward the normal level and the acidosis had entirely disappeared on the following day. Another case of coma is illustrated in chart 11. The patient was a man, aged 37 years, with a blood sugar content of 638 mg per hundred cubic centimeters, plasma carbon dioxide, 11.8, heavy acetonemia and acetonuria, and extremely heavy lipemia—the plasma being literally thick with fat.

¹ John, H. J. Diabetic Coma Complicated by Acute Retention of Urine, *J. A. M. A.* 84:1400 (May) 1925.

like 20 per cent cream. He received on three successive days 500, 190 and 80 units of insulin, respectively, 2,150 cc of 10 per cent dextrose was given on the first day, and 1,125 cc on the second day. The even fall of blood sugar on the first day, the maintenance of the lowered content on the second day, and the slight rise on the morning of the third day show clearly that the blood was not embarrassed by the added dextrose. With the decrease in the blood sugar content, the carbon dioxide curve rose rapidly, and in thirty-six hours the lipemia entirely disappeared.

Coma is a serious condition and requires one to take advantage of every possible measure, therefore the importance of immediate hospitalization cannot be overemphasized. Operations used to be done on the kitchen table in the home, but this is now done only in cases of extreme emergency. In the treatment of patients with coma, physicians are still living in the "kitchen table era," but this period will surely pass, just as it did in surgery, and then more persons with coma will be saved.

Von Noorden and other authors have called attention to the edema that occasionally follows or rather begins to develop during coma. It is probably due in part to insulin and in part to the partial suppression of urine by the kidneys. In 1925, I reported⁴ a marked case of this type, and at present I have a patient with a similar case in the hospital. The edema disappears, however, as the patient's condition improves.

BLOOD SUGAR RESPONSE TO INSULIN

Normal blood sugar values while a patient is fasting range from 70 to 120 mg per hundred cubic centimeters. Usually after a meal there is a slight rise in the blood sugar (up to 140 or 180 mg) with a quick return to normal (within one or two hours), this process being repeated after each meal. This postprandial rise is higher and more prolonged in diabetic patients. Taking advantage of this characteristic, for several years I have preferred to examine a patient by making an estimation of the blood sugar two and one-half hours after he has eaten a heavy carbohydrate meal. The important fact should be borne in mind that the blood sugar during fasting often fails to reveal diabetes in mild or borderline cases and even occasionally in a severe case. Any diabetic person on a proper diet can present a normal blood sugar content while fasting, but a diabetic person cannot present a normal blood sugar two and one-half hours after eating a heavy carbohydrate meal.

If hourly examinations of the blood sugar of a patient who is fasting all day are made, a slight fluctuation will be noted. This condition occurred in blood sugar tests made on me hourly from 8 a m to 5 p m on two days seven months apart (see *B* and *C* in chart 4). In several other observations which I made, these variations were not so marked.

These variations are much more pronounced in a fasting diabetic patient, the blood sugar sometimes varying from 124 to 206 mg per hundred cubic centimeters (see *A* in chart 4). Bearing in mind these fluctuations which occur normally in all persons, one should avoid considering as important changes in the blood sugar of from 4 to 12 mg per hundred cubic centimeters.

That administration of insulin effects extreme variations in blood sugar is shown in the three observations recorded in chart 5. The first patient (*A*) came to the hospital with a blood sugar content of 732 mg

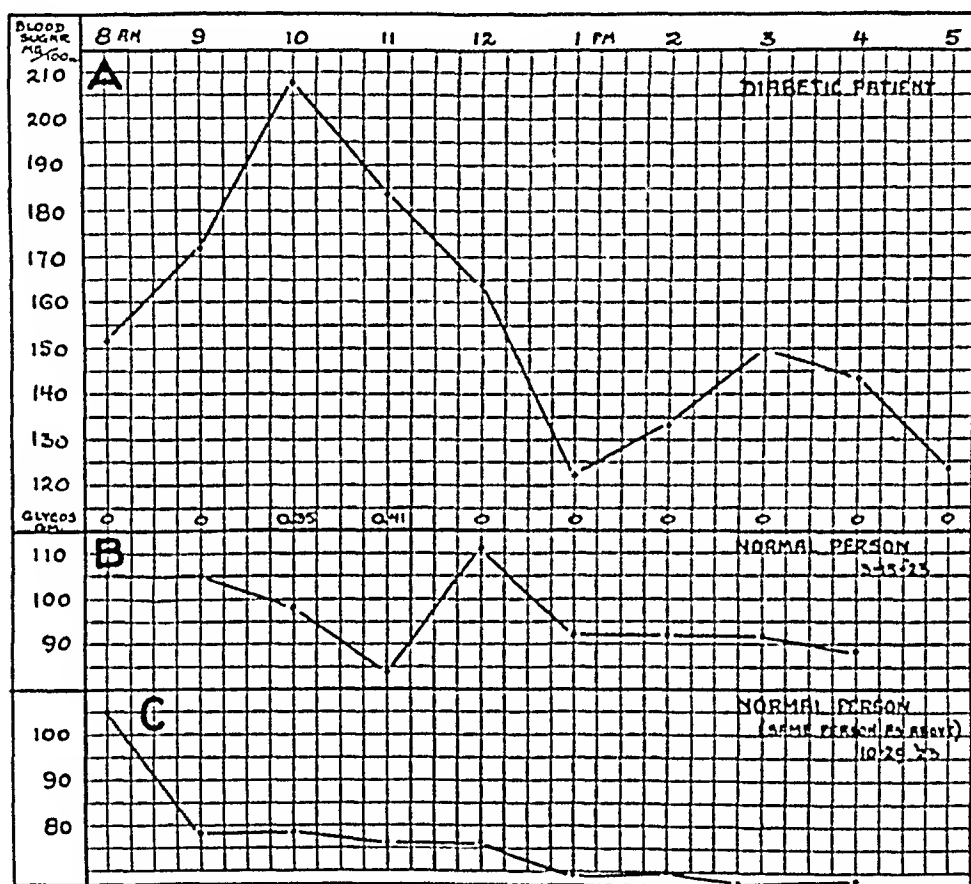


Chart 4—The fluctuations of the blood sugar level during fasting from 8 a. m. to 5 p. m. in a diabetic patient (*A*) and in nondiabetic persons (*B* and *C*)

per hundred cubic centimeters. It took eight hours and the administration of 160 units of insulin to reduce the blood sugar to the normal level, 122 mg per hundred cubic centimeters. The blood sugar level when the first dose was given was 624 mg. The response quotient of fall in blood sugar per hour per unit of insulin as illustrated by this case is found as follows: $624 \text{ (level when first dose was given)} - 122 \text{ (normal level reached)} = 502 - 8 \text{ (hours)} = 62.75 - 160 \text{ (insulin units)} = 0.39$

In this case, the fall in blood sugar in the first hour (from 732 to 624 mg) when insulin was not taken should be noted. The quotient

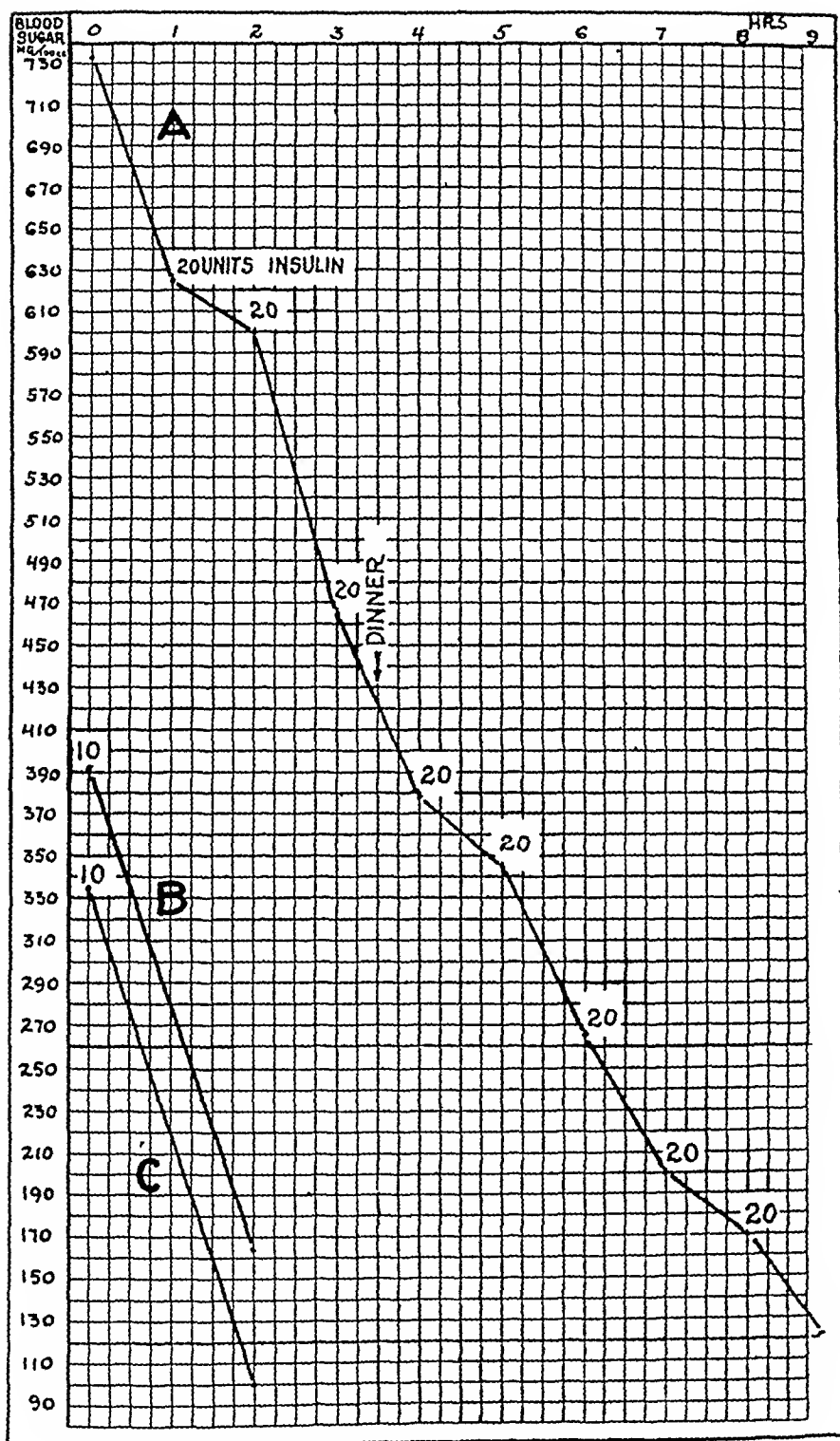


Chart 5—Response of blood sugar to insulin in three different diabetic patients

calculated by the same formula gives 114 and 112, respectively, for *B* and *C* in chart 5, results which show what a large variation there is in reaction to insulin in different persons. In the case recorded in chart 6, the same observation is made. A woman, aged 49 years, in whose case

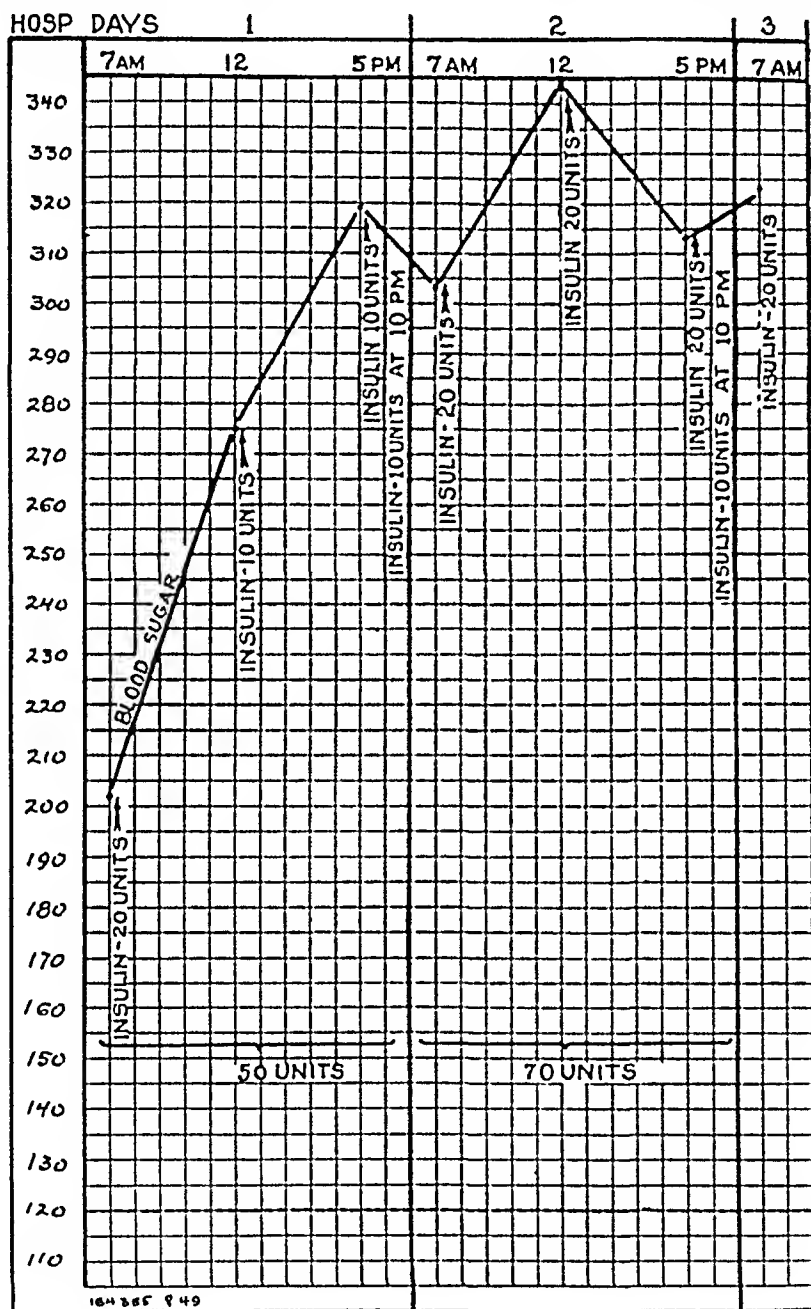


Chart 6—The variation in response of the blood sugar content to insulin on two successive days in the case of a diabetic patient, aged 49 years. The higher content on the second day should be noted.

observations were made on two successive days while she was on an identical diet, took 50 units of insulin in four doses on the first day and 70 units in four doses on the second day at the hours indicated on the

chart Though the patient received more insulin on the second day the effect on her blood sugar which had risen somewhat, was not at all proportional to the dose of insulin which she had taken

By observing the accumulative data of an individual case on a number of successive days, during which the dosage of insulin has increased with

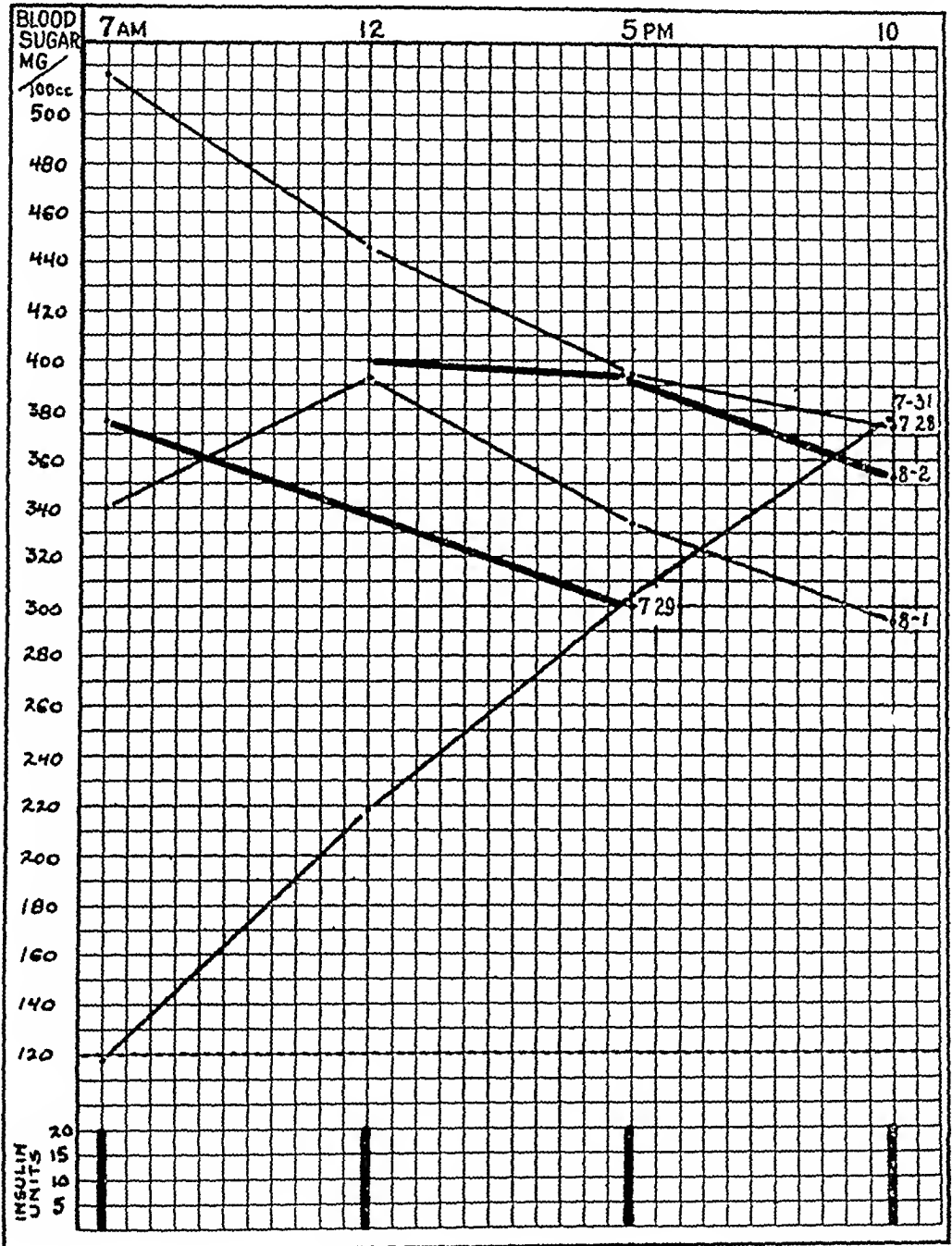


Chart 7—Variations in the response of the blood sugar content to identical doses of insulin in a diabetic patient on five successive days

each succeeding day, one can see that there is marked variation from day to day. The patient, the accumulative data in whose case are given in chart 7, received 20 units of insulin four times a day at 7 a. m., 12 m., 5 p. m. and 10 p. m. The dates of observation are given at the

end of each curve, and extreme variation may be noted from day to day. The observations made on the same patient when the insulin dosage was increased to 25 units four times a day are represented in chart 8. Continued observations of the same patient for two successive days in which

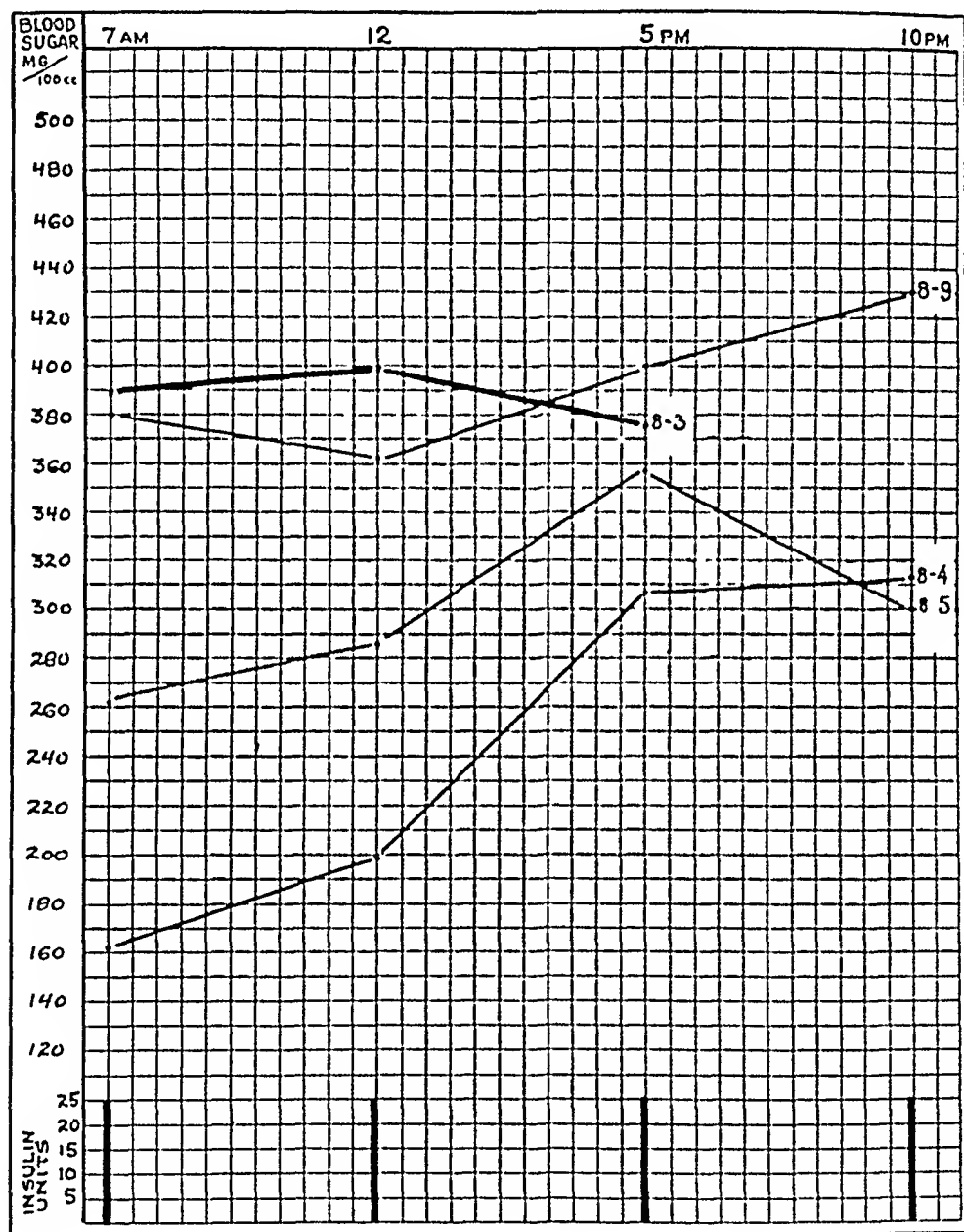


Chart 8—Variations in the blood sugar content of the same patient whose blood sugar curve is shown in chart 7 under an increased dosage of insulin

the dosage of insulin was markedly increased (120 units on the first day and 200 units on the second day) are shown in chart 9

Such fluctuations in blood sugar are not the rule, and yet they are not rare. Usually, diabetic patients respond readily to treatment with insulin,

but in severe cases such fluctuations as shown in these charts characterize a slow, uneven progress of the patient, if the routine treatment, however, is faithfully carried out for a long period, sooner or later the blood sugar will drop and will remain at a low level. I sometimes call this living according to routine "the wearing out process," because the patient has to wear out the diabetic hyperglycemia in order to establish a normal state. The surprising characteristic of this treatment is that once the normal status has been reached, a remarkably small amount of insulin is required to keep the patient's blood sugar at a low level.

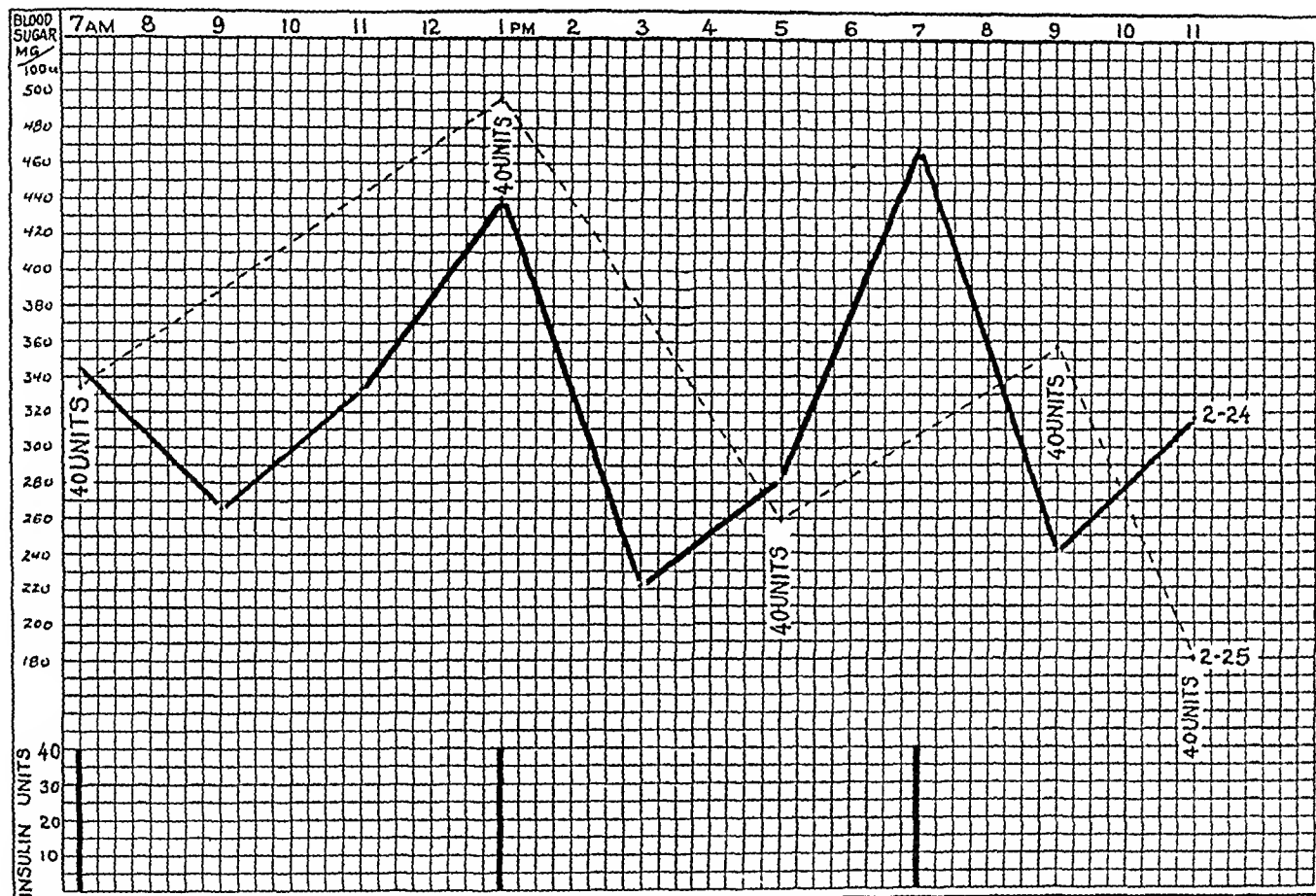


Chart 9—Variations in the blood sugar content of the same patient whose blood sugar curves are given in charts 7 and 8 on the same routine but under a markedly increased dosage of insulin

REACTIONS TO INSULIN

There is little that I can add to what I have already stated on the subject in my previous publications, except to cite a reaction which shows a higher figure than any which I was able to report in 1927. This reaction occurred in a woman, aged 30, whose blood sugar was 467 mg per hundred cubic centimeters at the time of the reaction.

Another observation that I am able to include in this report is one which I have never seen mentioned by any author, namely, a reaction

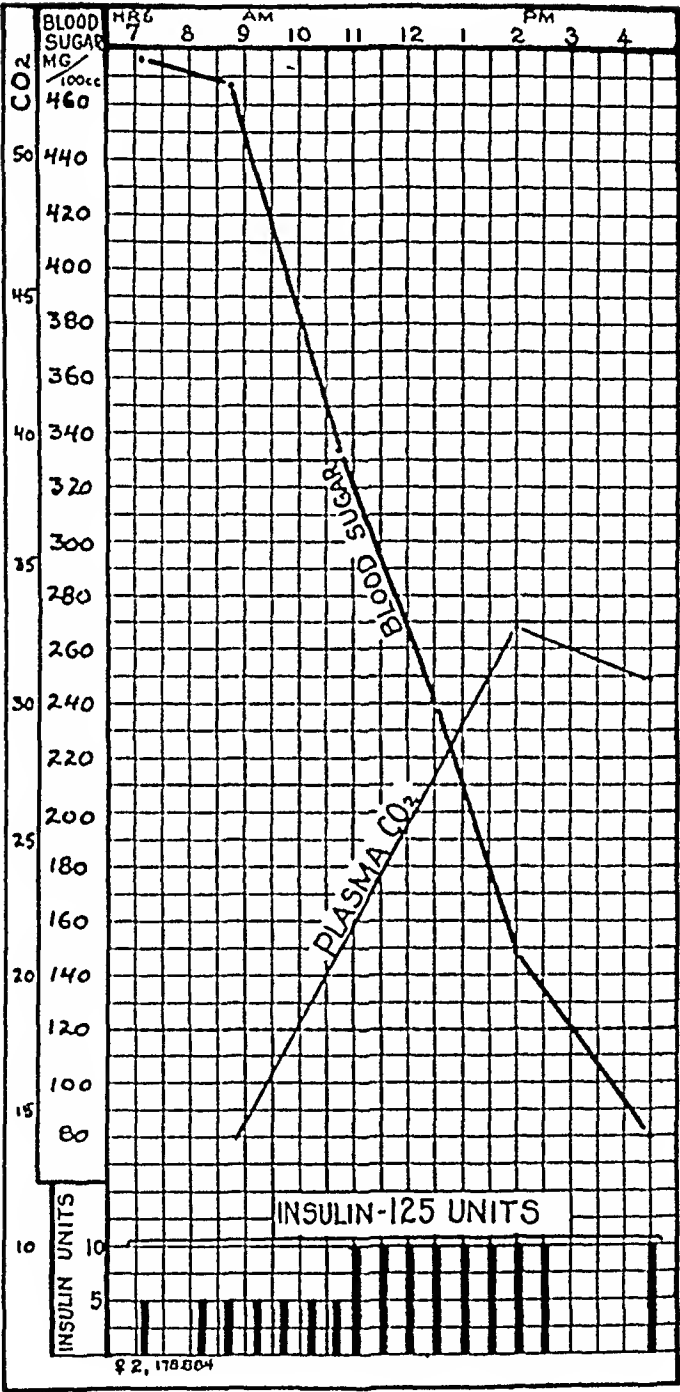


Chart 10—The response of blood sugar and of plasma carbon dioxide to insulin in a case of coma in a girl, aged 2 years

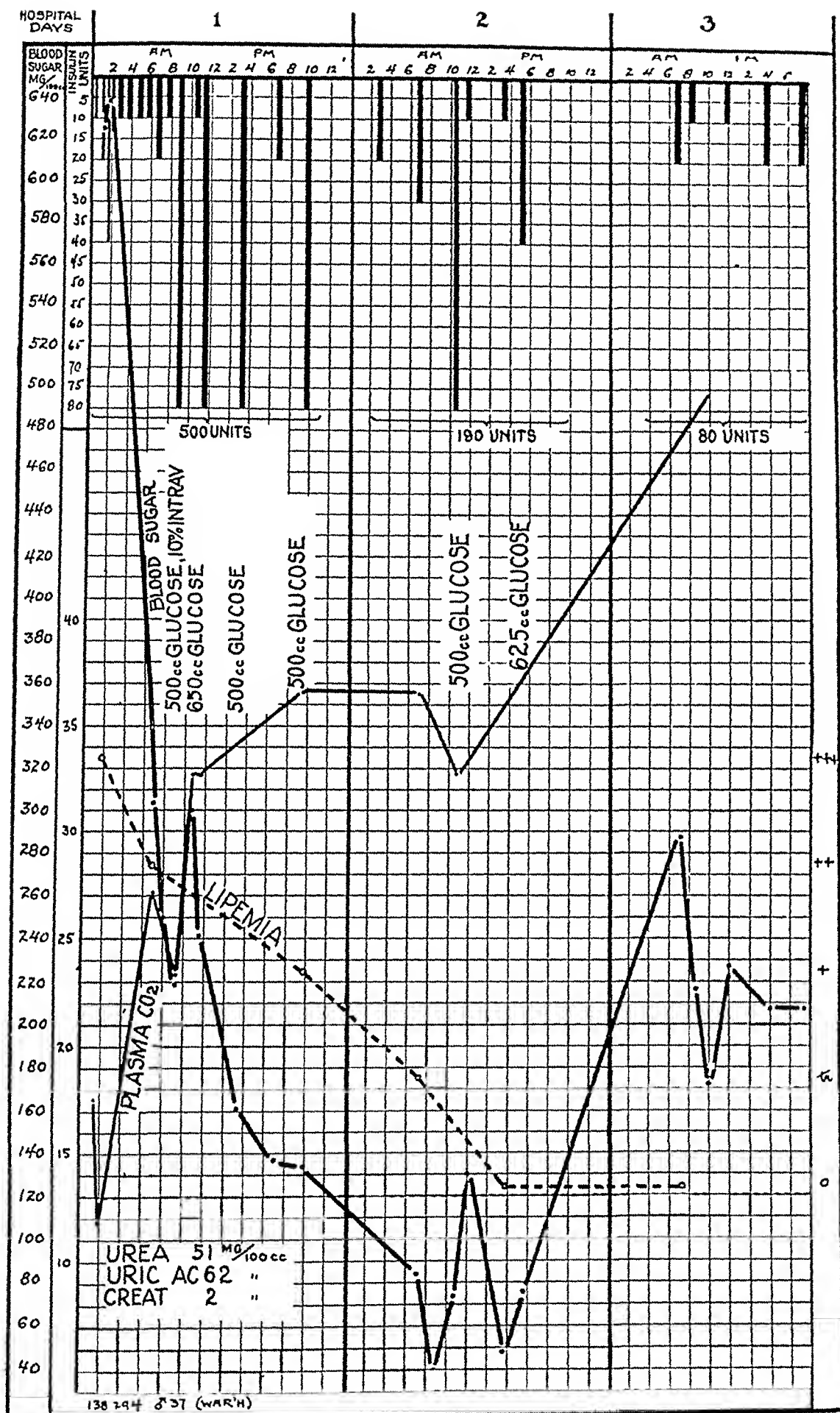


Chart 11 The response of blood sugar plasma carbon dioxide and lipemia to insulin in a case of coma in a man, aged 37 years

which was accompanied by a noticeable engorgement of the breasts and protrusion of the nipples

Insulin reactions cannot be attributed to hypoglycemia alone, for there are many normal persons in whom the blood sugar is as low as from 30 to 60 mg per hundred cubic centimeters who are not even conscious of anything unusual. Recently, I have analyzed 22,808 estimations of blood sugar in nondiabetic persons. If one takes time to peruse the figures given in that report, one will be strongly impressed with the fact that insulin reactions are not due to hypoglycemia alone.

Foshay⁵ brings out the fact that while hyperglycemia may be found in the plasma or whole blood during such a reaction the blood corpuscles are deprived of sugar. He thinks that this fact may account for the condition.

DIAPHRAGM AND SURGICAL OPERATIONS

Surgical operations on diabetic patients are not dreaded as they were formerly, and the statistics of mortality show improvement each year. No longer is the moribund patient taken to the surgeon as "the last resort," for as the rational therapy of diabetes is more universally recognized, the physician and the patient alike realize that a diabetic person can be operated on successfully as shown in chart 12.

The decreased mortality in operations on diabetic patients is due not only to the improved method of treatment, but also to a number of variable factors. The patient is no longer starved before the operation and his vitality thereby reduced, he is better fed and insulin is given in sufficient amounts to insure proper utilization of his food, thus enabling him to store away some glycogen in the liver. This factor alone is important in the postoperative convalescence of the patient. Another factor of like importance is the psychologic condition of the patient. He no longer needs to feel that a surgical procedure is a desperate procedure of last resort, he can submit to it with a feeling of assurance and hope. When he is free from pain plenty of liquids and fruit juices are given by mouth or physiologic sodium chloride solution by hypodermoclysis, or both, if the patient cannot take food by mouth dextrose is given intravenously (500 cc of a 10 per cent solution, with from 20 to 40 units of insulin). In this manner the patient may be tided over for days or even weeks. In one of my own cases which I have reported elsewhere, a patient in whom a cholecystenterostomy was performed was treated in this manner for a period of seven days, receiving dextrose and 20 units of insulin twice a day. Throughout this period the patient's blood sugar remained normal, and she felt well and was in excellent spirits. As already stated a physician should not hesitate to administer dextrose intravenously lest the blood sugar rise, for if sufficient insulin is given, the blood sugar will not be raised but usually will be consider-

5 Foshay, Lee. *Am J Physiol* 73:470, 1925.

ably lowered In table 15 of my former report,¹ wherein I have reported thirty-seven observations of the changes in blood sugar which have followed the intravenous administration of dextrose after operations on diabetic patients, the figures speak for themselves and prove that in

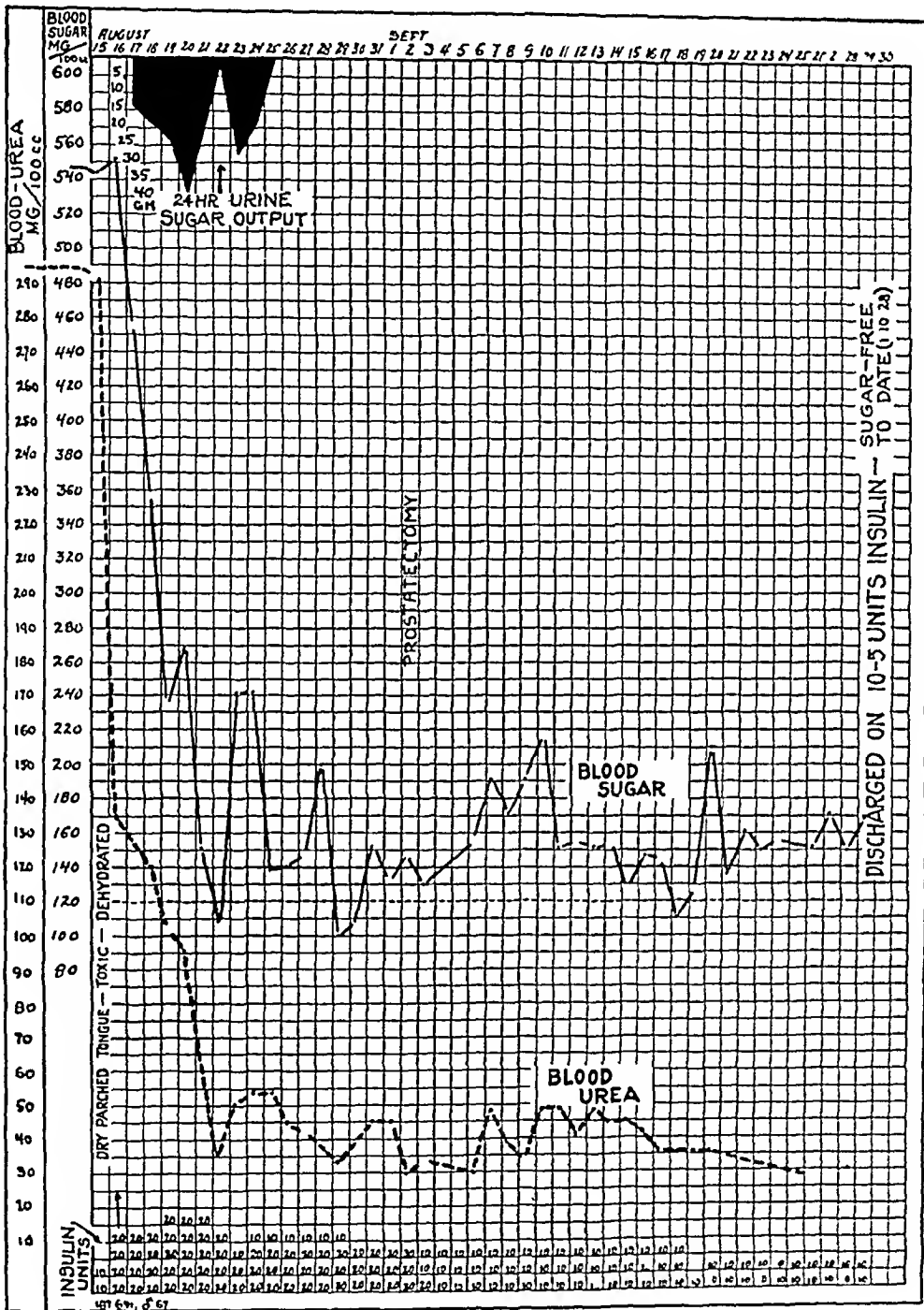


Chart 12—A chart illustrating the progress and treatment in a severe case of diabetes in a patient, aged 67 years, showing the routine before and after operation

severe and complicated cases such a procedure should be considered as a routine practice rather than as a measure of last resort

The diet of patients who have been operated on in whom diabetes is present is a subject worthy of particular notice The average diabetic

TABLE 11—Operations Performed on Diabetic Patients in the Cleveland Clinic Hospital^{*}

Major Operations	First Series		Second Series	
	No. of Patients	Died	No. of Patients	Died
Mistoidectomy	1		1	
Amputation of leg	10	1	4	2
Prostectomy	2		19	4
Thyroidectomy	12	4	6	5
Lobectomy			20	1
Removal of breast	1		5	1
Herniotomy			2	
Resection of colon			1	1
Hysterectomy			7	
Appendectomy			5	
Delivery			1	
Gastro-enterostomy			1	
Drainage of gallbladder			1	
Excision of diverticulum of bladder			1	
Gastric resection			1	1
Tracheotomy			1	
Laparotomy exploratory		1	7	1
Nephrectomy				
Resection of rectum			5	1
Colostomy			1	
Excision of umbilic			2	
Bone graft			1	
Cholecystectomy	1		6	
Amputation of cervix uteri			1	1
Resection of rib		1		
Resection of cecum for cancer	1			
		7	7	18
	Mortality	per cent 15	Mortality	per cent 22
Minor Operations				
Closure of rectal wound			1	
Resection of nasal septum				
Resection of nasal polyp			2	
Repair of hernia			2	
Cystoscopy			2	1
Amputation of toe or finger			6	
Cauterization of lip			1	
Excision of binion			1	
Lensectomy			1	
Incision of palmar fascia			1	
Incision of abscess			6	
Urethrotomy			1	
Blood transfusion			2	
Incision and drainage of chloroform abscess			2	
Hemorrhoidectomy			1	
Tonsillectomy			1	1
Ligation (thyroid)			27	
Prostatic punch operation			1	
Skin graft			1	
Dilatation and curettage			2	
Suprapubic puncture			2	1
Perineal repair			1	
Resection lipoma			1	
Cataract and iridectomy				
Incision of glands of neck			1	
		0	57	
	Mortality	per cent 0	Mortality	per cent 44
Total	25	7	276	21
Mortality percentage		28		7.6
Corrected mortality percentage		8.5		4
Average percentage, both series			64	

^{*} Omitting deaths from nonsurgical cancer

patient can do well on a diet yielding from 1,800 to 2,000 calories a day and containing carbohydrates, from 80 to 100 Gm and protein, from 50 to 70 Gm. On this diet, however, the patient would lose weight if his basal metabolic rate were increased, as is the case in hyperthyroidism. In such a case, a higher caloric diet and perhaps more insulin is needed—a need which must be determined for each patient. In active hyperthyroidism I use, for instance, a diet yielding 3,000 calories and containing 120 Gm of carbohydrate and 70 Gm of protein. This allows a liberal assortment of food, and the patient is not even conscious—and he should not be—that he is on a diet. To get the best results in the treatment of patients with hyperthyroidism, the physician must relieve

TABLE 12—*Operative Mortality in Diabetic Cases (Data Compiled from Literature)**

Author	Year	Number of Operations	Mortality per Cent
Adams and Wilder (Wiseonsin M J 22 557, 1924)	1924	27	1.2
John (J Lab & Clin Med 9 626, 1923-1924)	1921-1927	311	6.4
Lahey (Cited by Joslin, The Treatment of Diabetes Mellitus, 1916)		11	7.1†
Berkman (Lancet 36 303, 1916)	1915	26	7.6
Joslin (The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1916, p 128)	1919	61	9
Karewski (Deutsche med Wchnschr 40 8, 1914)	1914	68	11.8
Young (Boston M & S J 188 767, 1923)	1918-1922	99	16.1
Joslin	Before 1917	27	18
Weeden (J A M A 82 1165 [April 12] 1924)	1897-1922	12	16.6‡
Binney (Cited by Joslin, p 617)	1916-1923	22	19
Morrison (Boston M & S J 175 54, 1916)	1896-1913	77§	27
Jones (Boston M & S J 188 483, 1923)	1923	8	2.5
Fitz (M Clin N Amer 3 1107, 1920)	1918	45	30
Strouse	1916	28	21
Weeden	1897-1922	169	26.8
Foster (J A M A 84 572 [Feb 12] 1925)	1925		45.8
Mugund	1921	5	80

* Arranged in order of mortality percentages

† Thyroid cases

‡ Insulin cases

§ Statistical report from several hospitals

the hyperexcitable and nervously unstable patient of all unnecessary anxieties. There need not be cause for worry if a logical routine changed and adjusted to meet the existing conditions, is faithfully carried out.

Before a patient leaves the hospital he should be instructed about his diet and the use of insulin if he needs to take it. All surgical skill fails if after a brilliant surgical result, the patient goes home and drifts into a more severe stage of diabetes, so that he is worse off than he was before the operation. The surgeon should therefore have the cooperation of the internist before, during and after the operation.

In this series of 2,000 cases of diabetes, I have summarized the statistics regarding surgical operation in table 11. Major operations were performed on 221 patients and minor operations on ninety patients—a total of 311 operations, an incidence of 15.55 per cent, the incidence of major operations being 11.05 per cent. This means that one out of

every nine diabetic patients had a major operation. The mortality of the major operations in the first series was 21.87 per cent and in the second series, 9.52 per cent. These figures include mortality from all causes—often nonsurgical.

DIABETIC MORTALITY IN GENERAL

Of the 2,000 patients with diabetes whom I have observed thus far (during seven years) 131 have died—a total mortality rate of 6.55 per cent. Of these, sixty-two patients died here at the hospital and sixty-nine died elsewhere. In table 13, I have summarized the statistics of mortality according to the causes of death and the ages according to decades.

While the total mortality is 6.55 per cent, if the deaths in the seventh, eighth and ninth age decades were excluded, because of the natural incidence of death in those periods, the mortality incidence would drop to 4.44 per cent. The heaviest mortality is in the sixth decade, in which the incidence of diabetes is also the highest. The seventh decade shows a high incidence of mortality as does the fifth decade. The varied direct causes of death in this series show, as Joslin pointed out, that most diabetic persons die of diseases other than diabetes. In my series, coma was the most frequent cause of death, however, as I have pointed out in the section on coma, most of the patients who died in coma died at home where they received either faulty or insufficient treatment. Deaths from this cause will be fewer, no doubt as time goes on and as physicians generally appreciate increasingly the necessity of pushing rather than of discontinuing the use of insulin when coma occurs. I wish to emphasize therefore, the fact that it is easy to differentiate a diabetic coma from an insulin reaction.

THE INCIDENCE OF SYPHILIS IN DIABETES

A diabetic patient is not immune to other infections, and syphilis is no exception. In this series of 2,000 cases of diabetes, syphilis was present in fifty-four, or 2.7 per cent. A compilation of data from the literature is given in table 14. Joslin offered data on the largest series of cases of diabetes, namely on 3,200 patients; the incidence of syphilis in this series was 1.7 per cent.

In contrast to these low figures are the observations of Warthin and Wilson,⁶ who in six necropsies on diabetic patients at the University of Michigan found histologic changes characteristic of syphilis in all. In four of these six necropsies they were able to demonstrate spirochetes in the myocardium and in one patient also in the pancreatic lesions. In the Harvey Lectures of 1917-1919, Warthin offered an extensive discussion of this relationship. The observations of as keen an observer as Warthin make one wonder whether more extensive pathologic studies in patients with diabetes might not reveal much valuable information in this regard.

6 Warthin, A. S., and Wilson, U. F. *Am J M Sc* 152: 157, 1916.

TABLE 14—Incidence of Syphilis in Diabetes (Data Compiled from the Literature)

	Number of Cases of Diabetes	Number of Cases of Syphilis	Incidence Per Cent
Joslin (The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1916, p 128)	3,200	55	1.7
John	2,000	54	2.7
Williams (Cited by Joslin, p 605)	144	4	2.7
Rosenbloom (Cited by Joslin, p 611)	139	16	11.5
Smith (Virginia M Month 49 662, 1923)	79	2	2.5
Fitz and Murphy	50	5	10.0
Van Saun (Cited by Joslin, p 606)	12	1	1.3
Hirschfeld (Cited by Rosenbloom J A M A 68 1232 [April 28] 1917)			6.0

TABLE 15—Insulin Treatment and Progress of a Patient with Severe Diabetes

Date	Blood Sugar (Mg per 100 Cc)						Insulin Units							
	4 a m	7 a m	12 m	1 p m	5 p m	7 p m	11 p m	4 a m	7 a m	12 m	1 p m	5 p m	7 p m	11 p m
Aug														
15		543			535	550						10	10	
16		552	600	563	563				20	20		20		20
17		454	476		396				20	20		20		20
18		357	340		287		309		20	20		20		20
19	283	233	357		285		333	20	20	20		20		20
20	295	272	373		306			20	20	20		20		20
21		151	161					20	20	20		20		20
22		169		233		272		20	20		20		20	
23		241		340		360			20		20		20	
24		241				248			20		20		20	10
25		138	236		182				20	20		20		10
26		146			105				20	20		20		10
27		147							20	20		20		10
28		200							20	20		20		10
29		100							20	20		20		10
30		109							20		20		20	
31		152							20		20		20	
Sept														
1		132							20		20		20	
2		148	236		84				20		20		20	
3		130							20		10		10	
4									10		10		10	
5									10		10		10	
6		156							10		10		10	
7		191							10		10		10	
8		172							10		10		10	
9		191							10		10		10	
10		217							10		10		10	
11		151							10		10		10	
12		154							10		10		10	
13		152							10		10		10	
14		153							10		10		10	
15		127							10		10		10	
16		147							10		10		10	
17		143							10		10		10	
18		110							10		10		10	
19		125		150		132			10					
20		210							10				10	
21		136							10				10	
22		161							10				10	
23		159							10				10	
24		155							10				10	
25									10				10	
26		152							10				10	
27		171				227			10				10	
28		150				245			10				10	
29		169							10				10	

SUMMARY

- 1 A series of 2,000 cases of diabetes is reported in this paper
- 2 The incidence of diabetes among all diseases seen at the Cleveland Clinic during the period covered by this report has been 2.28 per cent
- 3 In this series, 46.75 per cent of the cases were in males and 53.25 per cent in females
- 4 The relative age incidence from the highest to the lowest according to age decades was as follows—sixth, seventh, fifth, fourth, third, second and first
- 5 In this series there was an hereditary history of diabetes in 5.3 per cent and a familial history in 4.5 per cent
- 6 The highest blood sugar level on admission was 908 mg per hundred cubic centimeters
- 7 Glycosuria was found in many diabetic persons with normal blood sugar (in 159 patients with blood sugar below 180 and in twenty-six with blood sugar 120 or below). On the other hand, glycosuria was not found in many patients in the presence of high blood sugar, the highest blood sugar level without glycosuria being 390 mg per hundred cubic centimeters
- 8 The general belief among the laity that insulin once used must always be continued is shown to be fallacious
- 9 The blood sugar response to insulin varies tremendously, as is shown in charts 3 to 8. It also varies widely from day to day in the same case
- 10 Insulin reactions are not wholly due to hypoglycemia, but are found fairly frequently in the presence of hyperglycemia, as noted in one case in which the blood sugar at the time of the insulin reaction was 467 mg per hundred cubic centimeters. Many normal persons have a blood sugar content as low as from 30 to 40 mg per hundred cubic centimeters
- 11 The total number of patients with diabetic coma in this series was eighty-five, or 4.25 per cent. Of the fifty-nine patients with coma that I treated, forty-eight lived (81.35 per cent) and eleven died (18.65 per cent). The causes of death are given in table 13. In these cases the blood sugar on admission ranged from 200 to 1,664 mg per hundred cubic centimeters, the plasma carbon dioxide ranged from 9.9 to 44.3, the highest figures appearing in patients who had received insulin before they were admitted
- 12 The total mortality in this series was 131, or 6.55 per cent
- 13 The total number of operations in this series was 221. Total mortality among the surgical cases was 12.66 per cent, the corrected mortality (after eliminating other causes of death) was 6.4 per cent
- 14 The incidence of syphilis in this series was 2.7 per cent

THE EFFECTS OF MORPHINE AND ETHER ON THE FUNCTION OF THE KIDNEYS*

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In the experiments herein described, data were obtained concerning the influence of morphine and ether, separately and together, on the function of the kidneys, that is, on the rate and composition of the urine secreted. It has been known for a long time that anesthesia diminishes the volume of urine secreted, and data exist also concerning the effect of anesthetics on metabolism in general, as represented by the composition of the urine, but we were unable to find a detailed study of the effects of anesthesia on the function of the kidneys.

METHOD

In order to eliminate all extraneous influences in the experiments, such as operative procedures, dogs with fistulas in the bladder were employed. The bladder was largely excised and the cut margin sewed into the skin. Healing required about a week, after which the animal was placed on a table with the opening in the fistula over a funnel, the rim of which rested in a hole in the table top, and the urine as excreted was collected in a cylinder beneath.

The quantity of urea was determined by the method described by one of us¹ and the quantity of chlorides by the Volhard-Arnold method or gravimetrically.

RESULTS OBTAINED WITH ETHER ALONE

Table 1 shows that in ether anesthesia there is either a complete cessation in the formation of urine or a decided oliguria. This, in itself, is not especially new, but the effect on the urea and chloride concentrations of the urine excreted is interesting. The data indicate that the capacity of the kidney to concentrate urea is diminished by ether, from 4 to 5 per cent being the maximum reached, and it may be lower in spite of the small quantity of urine secreted. If the urea concentration is low in the control period, it may rise under ether anesthesia but never to a concentration often reached under normal

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1 Stehle J Biol Chem **51** 89, 1922

conditions. In view of the well demonstrated fact—that in ether anesthesia the blood becomes decidedly concentrated (caused apparently by the passage of fluid from the plasma into the tissues), one might expect that even though the volume of urea excreted is small its concentration should be high if the filtration-reabsorption theory regarding the secretion of urine is correct. That is, one might expect that the increased demand of the tissues for water (as represented by a high blood concentration) would result in a better tubular reabsorption of water but this expectation is not fulfilled.

TABLE 1—*Effect of Ether Anesthesia on the Function of the Kidneys*

Experiment	Period	Time of Collection	Volume per Minute Cc	Mg. Excreted per Minute		Percentage Composition	
				Urea	Chloride	Urea	Chloride
13*	Control	1 55-2 45	1 11	6 25	0 193	0 563	0 017
	Ether	2 47-3 55	0 00	0 00	0 000	0 000	0 000
	Post Ether	4 47-5 27	0 09	1 00	0 037	1 11	0 041
	Post Ether	5 53-6 23	1 03	8 04	0 057	0 761	0 005
		(100 cc of water at 5 40 [by stomach tube])					
14*	Control	1 21-2 11	0 834	14 3	1 06	1 72	0 127
	Ether	2 20-3 20	0 085	3 77	0 128	1 13	0 150
	Post Ether	3 20-4 00	0 112	7 55	0 105	6 75	0 094
	Post Ether	4 38-5 18	0 139	10 0	0 052	7 20	0 037
15	Control	1 01-1 41	0 593	14 0	0 655	2 36	0 110
	Ether	2 00-2 50	0 128	4 09	0 301	3 20	0 308
	Post Ether	4 22-4 52	0 213	10 2	0 284	1 79	0 131
16	Control	1 05-2 05	0 068	5 07	0 067	7 16	0 099
	Post Ether	4 40-5 30	0 076	5 60	0 066	7 38	0 087
17	Control	12 50-1 40	0 121	7 15	0 406	5 91	0 336
	Ether	2 15-3 15	0 027	0 417	0 017	1 54	0 063
18	Control	12 20-1 10	0 132	11 5	0 82	8 72	0 623
	Ether	1 15-2 25	0 077	3 55	0 21	1 60	0 271
	Post Ether	4 34-5 24	0 170	12 2	0 39	6 97	0 222
	Post Ether	8 16-8 57	0 127	6 95	0 84	5 46	0 662
19	Control	2 18-3 08	0 166	6 57	0 42	3 90	0 253
	Ether	3 22-4 22	0 066	1 65	0 15	2 50	0 228
	Ether	4 22-5 02	0 105	3 62	0 21	3 15	0 200
20	Control	1 04-1 44	0 168	6 89	0 212	4 10	0 127
	Ether	1 54-2 54	0 00	0 00	0 000	0 00	0 000
	Post Ether	3 53-4 23	0 210	7 68	0 364	3 66	0 17
	Post Ether	5 16-5 46	0 397	14 8	0 129	3 73	0 108

* In experiments 13 and 14, water was given by mouth about one hour before the collection of urine was begun. In the other experiments in this table, water was not given.

In order to explain the observations on the basis of the filtration-reabsorption theory, the results in those experiments in which some secretion occurs require one to assume that tubular reabsorption of water is diminished by ether—otherwise the concentration of urea would not be diminished, and in the experiments in which total suppression of urine secretion occurs, they appear to require that no filtration occurs, else why should the secretion of urine cease? This amounts to assuming what would appear to be highly improbable that ether abolishes the flow of blood through the kidneys for there is

not any other apparent reason why, on the basis of the filtration reabsorption theory, no urine should be excreted

Much the same phenomenon occurs with regard to the excretion of chlorine as in the case of the secretion of urea. If the chloride concentration is low in the beginning, the concentration may rise under anesthesia, but when the initial concentration is high anesthesia causes

TABLE 2—*Effects of Morphine on the Function of the Kidneys*

Experiment	Period	Time of Collection	Volume per Minute Cc	Mg Excreted per Minute			Percent age Composition	
				Urea	Chloride	Phosphorus	Urea	Chloride
1	Control	2 40-3 10	1 68	7 64	0 348	0 066	0 455	0 021
	Morphine	3 30-5 10	0 117	5 08	0 166	0 068	4 34	0 142
2	Control	10 59-11 40	1 51	10 2	0 27	0 170	0 676	0 018
	Morphine	11 30-2 00	0 230	7 66	0 58	0 071	3 33	0 252
	Ether	2 00-3 00	0 70	7 35	2 40	0 166	1 05	0 343
3	Control	1 35-2 05	2 40	11 7	1 64	0 035	0 487	0 068
	Morphine	2 27-3 07	0 264	10 3	0 94	0 091	3 90	0 355
	Ether	3 15-4 25	0 24	5 97	0 47	0 673	2 49	0 283
4	Control	1 53-2 33	0 920	10 4	0 796	0 284	1 13	0 087
	Morphine	2 34-3 44	0 071	1 86	0 054	0 087	2 62	0 076
	Ether	3 49-4 39	0 15	4 84	0 085	0 452	3 23	0 057
Post	Ether	4 59-5 39	0 19	8 25	0 136	0 433	4 34	0 072
5	Control	1 39-2 09	2 07	8 98	0 310	0 294	0 434	0 015
	Morphine	3 23-3 48	0 136	2 70	0 176	0 175	1 09	0 129
	Ether	4 07-5 22	0 05	0 52			0 104	
	Ether	5 22-5 54	0 24	5 71	0 207	0 467	2 38	0 086
6	Control	2 40-3 10	0 170	7 87	0 125	0 085	4 63	0 074
	Morphine	3 21-4 01	0 190	9 44	0 544	0 054	4 07	0 286
7	Control	1 25-2 05	0 110	8 58	0 085	0 131	7 80	0 077
	Morphine	2 15-3 05	0 117	8 92	0 153	0 053	7 63	0 131
	Ether	3 05-4 55	0 51	10 5	0 674	0 158	2 06	0 132
8	Control	1 31-2 21	0 099	8 62	0 049	0 034	8 71	0 056
	Morphine	2 31-3 21	0 081	8 21	0 083	0 012	10 1	0 103
	Ether	3 21-4 31	0 049	2 85	0 057	0 085	5 81	0 117
	Ether	4 31-5 41	0 064		0 011	0 327		0 017
9	Control	2 10-3 00	0 164	6 16	0 48	0 095	3 76	0 293
	Morphine	3 10-4 10	0 045	2 68	0 129	0 027	5 95	0 287
	Ether	4 15-5 05	0 47	6 18	1 27	0 113	1 31	0 271
10	Control	1 45-2 45	0 101	6 98	0 146	0 061	6 91	0 144
	Morphine	3 05-4 05	0 043	4 07	0 050	0 031	9 46	0 116
	Ether	4 15-5 15	0 150	4 67	0 121	0 297	3 11	0 081
11	Control	2 33-3 13	0 102	8 58	0 645	0 164	8 41	0 634
	Morphine	3 42-4 42	0 045	4 51	0 121	0 025	10 0	0 269
	Ether	4 47-5 47	0 154	4 92	0 339	0 568	3 19	0 220
12	Control	1 30-2 10	0 22	11 2	1 15	0 355	5 09	0 524
	Morphine	2 32-3 32	0 11	8 68	0 328	0 143	7 89	0 295
	Ether	3 38-4 38	0 17	5 41	0 478	0 478	3 18	0 278

a fall in the amount and concentration of the chloride concentration of the urine

The results apparently indicate that a secretory mechanism is involved in the same sense as it is in the glands of the alimentary tract—that is, that urea and chlorine are actively secreted, not merely left over after a process of filtration and reabsorption, and that the comparatively low concentrations attained under ether merely indicate that the efficiency of the secretory process is diminished by anesthesia

RESULTS OBTAINED WITH MORPHINE ALONE

Under ordinary circumstances the effect of morphine on function of the kidneys is not marked (table 2). Usually there is evidence of a slight depression of function, but frequently no important effect is noticed. If, however, the initial rate of the secretion of urine is high, the administration of morphine causes a decided decrease in the volume of urine secreted but has much less effect on the quantities of urea and chlorine, so that the percentages of these constituents rise. To explain these results in terms of the filtration-reabsorption theory

TABLE 3—*Effect of Morphine on Rate of Excretion of Water and Urea after Administration of a Solution of Urea*

Experiment	Period	Time of Collection	Volume per Minute Cc	Mg Urea per Minute	Per Cent Urea	Remarks
21	Control	8 59-9 25	0 30	20 7	7 0	300 cc of 2 per cent urea solution at 9 27 10 mg of morphine sulphate per kilogram at 10 15
	After urea	9 48-9 58	3 43	51 8	1 51	
		9 58-10 03	4 60	52 2	1 14	
		10 03-10 07	5 13	51 7	1 01	
	After morphine	10 26-10 41	0 90	27 9	3 10	
	After morphine	10 41-10 59	0 53	29 8	3 62	
	After morphine	10 59-11 14	0 43	22 7	7 61	
22	Control	8 49-9 26	0 16	12 2	7 62	100 cc of 2 per cent urea solution at 9 50 10 mg of morphine sulphate per kilogram at 10 7
	After urea	9 49-10 09	0 43	21 4	1 98	
		10 09-10 24	0 64	21 5	3 36	
		10 24-10 36	0 62	20 7	2 33	
	After morphine	11 02-11 39	0 10	8 71	8 71	
	After morphine	11 39-12 08	0 13	12 6	9 69	
23	Control	9 17-9 47	0 135	13 1	9 71	200 cc of urea at 9 50, 10 mg of morphine sulphate per kilogram at 10 52
	After urea	10 18-10 33	1 30	30 8	2 37	
	After urea	10 33-10 49	1 50	28 1	1 87	
	After morphine	11 11-11 35	0 30	17 9	5 97	
	After morphine	11 35-12 01	0 40	23 6	5 90	
24	Control	1 33-1 59	0 133	6 63	4 70	175 cc of 2 per cent urea solution at 2 15 10 mg of morphine sulphate per kilogram at 2 57, 100 cc of 2 per cent urea solution at 3 46
	Control	1 59-2 14	0 090	4 87	5 43	
	After urea	2 48-2 57	5 0	23 4	0 47	
	After morphine	2 57-3 05	4 5	19 1	0 50	
	After morphine	3 05-3 16	1 45	15 1	1 03	
	After morphine	3 16-3 27	0 45	14 5	3 25	
	After morphine	3 27-3 45	0 26	19 1	7 49	
	After morphine	3 51-4 20	0 36	22 9	6 64	
	After morphine	4 20-4 36	0 40	20 5	5 22	
	After morphine	4 36-4 54	0 40	21 2	5 50	

one must suppose that under the influence of morphine the tubular reabsorption of water is facilitated. For example, in experiment 3 of table 2, the volume of urine is reduced from 2 4 cc per minute before the administration of morphine to 0 264 cc after its administration, with but slight effect on the rate of excretion of urea. Since in the period when morphine was given the rate of glomerular filtration (assuming for the moment that there is such a thing) must have been practically equal to that in the control period (as the rates of secretion of urea are nearly the same), it follows that tubular reabsorption must have been much more complete in the period after the administration of morphine than in the control period.

Again in experiment 24 (table 3), there is a striking decrease in the rate of volume after morphine, but the excretion of urea shows that glomerular filtration must be proceeding at not much less than the rate in the first period after urea was administered. Experiments 21 and 23 of table 3 are similar in this respect. In experiments 26 and 27 (table 5), in which the diuresis was produced by the intravenous administration of dextrose solution, morphine slows the rate of the excretion of water much more than that of urea.

If one regards increased tubular reabsorption as improbable, the only apparent alternative is to regard the secretion of water per se as having been depressed. Such a statement explains nothing, of course, but, on the other hand, it would seem rather improbable that morphine should increase tubular reabsorption in the kidneys.

TABLE 4—*Effects of Morphine on Absorption and Excretion of Water*

Amount of Water Introduced Cc	Time Left in Loop Minutes	Amount Withdrawn Cc
	Control	
40	10	18
40	10	25
40	10	27.5
30 minutes after 10 mg morphine per kilogram		
40	10	13
40	10	20
Ether anesthesia then introduced		
40	10	15
40	10	23
40	0	42

Several objections may be raised against the experiments themselves. It might be said that under morphine therapy there is a change in the composition of the blood, that is, a concentration. This is not the case, however, as indicated by the experiments of Bourne,³ who showed that the solid content of the blood is practically unaffected by morphine. The experiments of Bogert, Underhill and Mendel⁴ also showed that under the influence of morphine, intravenously injected Ringer's solution left the blood more slowly than in the absence of morphine, hence, so far as the effect of morphine on the composition of the blood is concerned, this substance should favor urinary secretion rather than retard it.

Since, in the experiments referred to, the initial diuresis was produced by the administration of water by mouth, the objection might be raised that morphine interferes with the absorption of water from the intestine. This has been tested directly in a dog with a Thiry-Vella fistula. Both openings were suitably closed during the period of

3 Bourne Brit J Anesth 2 1, 1924

4 Bogert Underhill and Mendel Am J Physiol 41 189, 1916

absorption, and at the end of the period as much of the remaining fluid as possible was withdrawn directly into a cylinder by means of a rubber catheter inserted into the fistula, a partial vacuum being created in the cylinder by a water pump. The results (table 4) do not support the idea that morphine, ether or both together interfere with this process.

The same point has been tested in another way. For example, a 2 per cent solution of urea is given by mouth instead of water and the effect of morphine on the rate of the secretion of water and urea is then determined. If under the influence of morphine this solution is absorbed as well or nearly as well as normally, and if the secretion of water is interfered with more than the secretion of urea, then the rate of secretion of urea should not be greatly affected after the administration of morphine, but its concentration should be considerably increased. Table 3 shows the results of four such experiments. In experiment 24 it will be seen that after morphine was given, urea continued to be excreted at a rate well above the rate of the control and at a decidedly increased concentration. The alternative explanation, namely, that morphine interferes with the absorption of water from the intestine more than with the absorption of urea, must be recognized, but it cannot be considered a potent objection. This is obvious because in experiment 21 it will be seen that after the administration of urea the urea concentration of the urine secreted was less than 2 per cent, which fact would indicate that water was more readily absorbed from the intestine than was urea. Experiments 21 and 23 are of the same general nature as experiment 24. In experiment 22 the results are not so convincing, but it will be noted that the urinary urea after the administration of morphine reached a concentration of from 8.71 to 9.69 per cent, which may represent the maximum concentration possible under the conditions of the experiment.

To eliminate the question of intestinal absorption entirely we have given Ringer's or isotonic dextrose solutions intravenously before administering the morphine. Table 5 shows the results. In experiments 26 and 27, decided increases in urea concentration were effected even though the minute rate of the secretion of urea was diminished. That the morphine does really influence the secretion of water by the kidneys may be seen from experiment 28 in which morphine was not given; here the high rate of volume excretion persists for a long time.

RESULTS OBTAINED WITH MORPHINE AND ETHER TOGETHER

It has been shown thus far that ether anesthesia alone is a decided depressant of function in the kidneys, and morphine also, though to a slight extent. Consequently it is rather surprising to observe that when ether anesthesia is induced after morphinization function of the kidneys

is decidedly better than when ether only has been administered. We have not observed any instance of anuria in morphine-ether anesthesia.

The formation of urine not only continues, but persists often to a satisfactory extent, as inspection of the data will reveal.

TABLE 5—*Results of Intravenous Administration of Ringer's or Isotonic Dextrose Solutions before Morphine*

Experiment 25						
Time of Collection	Volume per Minute Cc	Mg Excreted per Minute		Phosphorus	Percentage Composition	
		Urea	Chloride		Urea	Chloride
1 59-2 29	0 16	3 80	0 14	—	2 38	0 27
	2 35-2 40	240 cc of Ringer's solution intravenously				
2 44-2 58	0 59	6 91	4 94	—	1 17	0 84
2 58-3 18	1 33	7 20	9 36	—	0 51	0 63
3 18-3 38	2 13	7 32	11 6	—	0 35	0 52
	3 38-100 mg	of morphine sulphate subcutaneously				
3 38-4 00	2 01	7 28	9 3	—	0 36	0 46
4 00-4 20	1 01	6 98	5 85	—	0 69	0 55
4 20-4 30	0 77	6 62	4 66	—	0 86	0 61
4 30-4 45	1 01	7 05	5 5	—	0 68	0 53
Experiment 26						
	10 30-200 cc	of water by mouth				
2 40-2 50	0 61	10 1	0 78	—	1 65	0 132
2 50-3 00	0 53	8 71	0 62	—	1 64	0 118
	3 00-3 15	250 cc of 5.4 per cent dextrose solution intravenously				
3 00-3 15	2 33	11 4	2 59	—	0 49	0 111
3 15-3 19	6 75	10 3	9 83	—	0 15	0 108
	3 19-100 mg	of morphine sulphate subcutaneously				
3 19-3 30	3 6	8 38	3 56	—	0 23	0 098
3 30-3 42	1 1	4 40	0 22	—	0 57	0 028
3 42-4 07	0 32	6 15	0 15	—	1 92	0 047
4 07-4 20	0 22	5 90	0 09	—	2 71	0 043
Experiment 27						
	10 30-250 cc	of water by mouth				
2 02-2 32	0 29	4 83	6 127	0 178	1 65	0 044
	2 35-2 40	275 cc of 5.4 per cent dextrose solution intravenously				
2 32-2 41	4 6	9 98	6 5	0 157	0 217	0 14
2 41-2 44	11 0	8 07	16 0	0 237	0 072	0 15
	2 44-140 mg	of morphine sulphate subcutaneously				
2 44-2 52	6 0	6 26	5 25	0 147	0 104	0 088
2 52-3 10	2 0	4 45	0 32	0 035	0 219	0 158
3 10-3 30	0 30	3 19	0 20	0 019	1 08	0 066
	3 30-Ether anesthesia begun					
3 47-4 07	1 05	4 62	0 29	0 357	0 44	0 027
4 07-4 37	0 67	3 28	0 20	0 512	0 41	0 030
Experiment 28						
	3 00-3 10	250 cc of dextrose solution intravenously				
3 00-3 08	0 85	11 1	0 87		1 30	0 102
3 08-3 18	1 87	6 52	1 54		0 35	0 082
3 18-3 43	1 70	4 62	0 40		0 27	0 023
3 43-3 57	3 60	5 68	0 50		0 16	0 024
3 57-4 07	3 67	6 3	0 80		0 17	0 022
4 07-4 32	2 05		1 1			0 055
4 32-4 47	1 46	5 78	1 0		0 10	0 067
4 47-5 23	1 84		0 96			0 052
5 23-5 33	1 77	5 3	1 16		0 30	0 066

It is possible that the augmented secretion which results when ether anesthesia is superimposed on morphinization is a salt diuresis. In those instances in which an increased flow is most pronounced (table 2, experiments 2, 4, 7, 9, 10, 11 and 27) there is a greater excretion

of chlorine or orthophosphoric acid, or both. It has been shown in other experiments from this laboratory⁵ that ether and morphine acting together produce a large increase in the excretion of sodium, potassium and phosphoric acid, which result coincides with this explanation. Results already published⁶ indicate that pituitary extract causes the liberation of potassium and sodium salts from the tissues and so causes salt diuresis, it may be that ether, acting after morphine, produces a similar effect. The accelerated excretion of salts is accompanied by the excretion of urea which, doubtless, would not have been excreted under simple ether anesthesia.

Another explanation, and possibly a more likely one, is as follows. The amount of ether necessary to produce anesthesia in narcosis due to morphine is less than when ether only is used. Consequently, the depression of the function of the kidneys by the ether is less marked, and a degree of activity more closely approaching that observed in narcosis due to morphine is observed.

Experiments recently described by Hames and Milliken,⁷ in which the secretion of indigo carmine during ether anesthesia with and without the previous administration of atropine and morphine was studied, are supported by our experiments. In fact, their results are more striking than our own, but we consider that a study of the extent to which the secretion of normal urinary constituents are affected is more illuminating than is the result obtained with indigo carmine.

SUMMARY

The effects of ether and morphine acting separately and concomitantly on the secretion of water, urea and chlorides by the kidneys have been studied. The results appear to be difficult to interpret on the basis of filtration-reabsorption theory.

While, in general, when each of these substances acts alone kidney activity is diminished, it is shown that when they act concomitantly the amount of secretion is greater than it is with ether alone. Possible explanations for this result are suggested.

5 Stehle, Bourne and Barbour. *J. Biol. Chem.* **53** 341, 1922. Stehle and Bourne. *J. Biol. Chem.* **60** 17, 1924.

6 Stehle. *Am. J. Physiol.* **79** 289, 1927.

7 Hames, W. H., and Milliken, L. F. *Renal Function. Results of Experimental Work with Morphine and Atropin.* *J. A. M. A.* **85** 1853 (Dec. 12) 1925.

THE RELATION OF THE REACTION TO EPI- NEPHRINE TO THE POTASSIUM-CALCIUM RATIO AND OTHER RATIOS *

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During the course of investigations dealing with a correlation of skin reactions with the blood chemistry and certain cardiovascular renal reactions, we have had occasion to study the effect of subcutaneous injections of epinephrine on the blood pressure of one hundred so-called "normal" men, as well as on about fifty patients who were ill from various diseases (glaucoma, exophthalmic goiter and other conditions) It is our purpose to enter into an analysis of these correlations in this paper

It is agreed we believe, that the original efforts of Eppinger and Hess¹ to classify all persons into groups that were vagotonic or sympathotonic proved unsatisfactory, indeed confusing There is no doubt that the emphasis placed on the study of the autonomic reactions of the patient has contributed immensely to the concept of the underlying factors of a number of disease conditions, but this study has added, for the time being at least, much uncertainty as well Some of the confusion is due to the earlier concept that the autonomic apparatus consists merely of an equilibrated nervous mechanism with antagonistic impulses, to the pharmacologic aspect which has probably not infrequently failed to distinguish between direct protoplasmic action and selective action of the so-called autonomic drugs, to the fact that the cardiovascular response to epinephrine, for instance, need not be a criterion of its effect on other tissues The great dependence of the reaction of individual organs or tissues on their state of activity when the autonomic impulse might become operative, the importance of the endocrine and humoral ionic milieu has been almost wholly disregarded We seem warranted in believing at present that the original idea of Eppinger and Hess as to a one-sided preponderance of either the vagus or sympathetic nerve is incorrect, indeed, that when alterations do occur in the autonomic apparatus, both vagus and sympathetic nerves are involved, that when an apparent overbalance exists overcorrection is usually

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1 Eppinger, H, and Hess, L Ztschr f klin Med 68 205, 230, 1909

apparent either in the organ or in remote regions and that we deal not merely with an autonomic apparatus as such, but with more fundamental alterations in the cells of the organs, changes intimately associated with stimulation or rest, fatigue or even death.²

Partly as a result of the indefinite clinical observations which have been associated with the so-called vegetative neuroses, clinicians in general make little use of the tests designed to elucidate the preponderance of either vagus or sympathetic influence except in the study of the cardiac reactions. But in recent years the study of the electrolytes of the body, originating with Loeb and carried out in clinical directions particularly by the Kraus school³ (Zondek, Arnold, Wollheim, Diesel, Kylin) and others, has indicated the intimate connection between the presumptive autonomic reactions, the electrolyte balance and the hormones. Kylin, in particular, has devoted considerable time to the correlation of these alterations in the blood chemistry in asthma, hypertension, diabetes and other conditions to the reaction of epinephrine.⁴

As stated in the foregoing paragraphs, our material consisted, first of a group of one hundred normal persons. Of these, about twenty were laboratory workers, the rest were men sent to us from an employment bureau. They were normal in the sense that they were not patients and that they gave a cross-section of a male working population of varying ages. On closer analysis, however, the great majority were by no means absolutely normal. Of the total number, twenty-six were apparently normal in every sense, thirteen were apparently normal, but a well defined healed parenchymal tuberculosis was revealed by roentgen-ray examination. Then there were those cases in which active pulmonary tuberculosis was made probable by the roentgenogram, the cases with a positive Wassermann reaction, the markedly nervous persons, and a large group of persons who revealed cardiovascular-renal alterations, as shown by the blood pressure, roentgen-ray examination of the heart and large vessels, observations on the urine, microscopic examination of the capillaries of the skin, etc.

2 Because of the confusion resulting from the conflicts between anatomic nomenclature and classification of the autonomic nervous apparatus and the pharmacologic methods of analysis, Muller and one of us (W. F. P.) (*Arch. Int. Med.* **40**: 575 [Nov.] 1927) have used the term sympathetic status to denote organ activity associated with contracted vessels (i. e. usually tissue rest), while we have used the term parasympathetic status to denote tissue activity when the vascular channels are dilated (i. e. with stimulation of an organ). This is, of course, a purely functional point of view but one which we believe avoids certain of the present difficulties.

3 Kraus, F. in Zondek, S. G. *Die Elektrolyte, Ihre Bedeutung für Physiologie, Pathologie und Therapie*, Berlin, Julius Springer, 1927.

4 Kylin, E. *Acta med. Scandinav.* **66**: 197-206, 1927.

To this so-called normal material, there has been added a group of forty-nine patients from the wards of the Research Hospital. As so constituted there were

Normal persons	26
Normal, with healed parenchymal tuberculosis	13
	—
	39
Cardiovascular renal abnormalities	68
Among these were 7 with glaucoma	
5 with active tuberculosis	
2 who were nervous	
1 with syphilis	
1 with urticaria	
1 with angioneurotic edema	
Nervous or neuresthenic	9
Angioneurotic edema	1
Syphilitic	5
Tuberculous	5
Exophthalmic goiter	7
Eczema	2
Epilepsy	1
Scleroderma	1
Myasthenia gravis	1
Urticaria	1
Heart disease	1
Epidemic encephalitis	1
Cancer of the thyroid	1
Glaucoma	2
Bronchitis	1
Feminine type young male	1
Dwarf	1
Tumor of the brain	1
	—
Total	149

With some unavoidable degree of arbitrariness, we have divided these persons into ten groups according to the reaction of the systolic blood pressure following the subcutaneous injection of 0.5 cc of a 1:1,000 dilution of epinephrine. In the individual curves which are presented, the systolic blood pressure curve for one hour after the injection is shown.

The first five groups can be regarded as sympathetic in character. Seventy-six persons are represented in these groups.

The second series can be classified as parasympathetic, in that either the reaction was negative, or showed a depressor action, either primary or permanent. There were seventy-three in these groups.

In examining the charts and tables, it may be of interest to note that so-called normal persons are found in both the sympathetic and the parasympathetic groups, but there are more in the sympathetic groups. No normal person has responded with a marked or persistent fall in blood pressure. It may also be of interest to note that twice as many of the extuberculous persons (as shown by roentgen-ray examination) are to be found in the sympathetic groups.

In table 3 are presented the averages of results of the observations in the ten groups for the various examinations that were made on the persons examined.

TABLE 1—*Group of Persons Who Give Sympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Tx Tuberculosis	Cardiovascular Renal Disease
I	16	Immediate and sustained increase	1	2	9
II	19	Immediate increase, not sustained	1	0	8
III	15	Slow, sustained increase	3	1	6
IV	10	Slow rise, not sustained	2	1	7
V	16	Slight increase	6	2	6
Total	76		15	9	6

TABLE 2—*Group of Persons Who Give Parasympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Tx Tuberculosis	Cardiovascular Renal Disease
VI	24	Slight decrease	4	1	11
VII	14	More marked, slow decrease	0	0	8
VIII	14	First reaction down, recovery	3	0	4
IX	11	Similar to VIII	3	2	5
X	10	More marked primary drop, recovery	1	1	4
Total	73		11	4	2

In table 4 A, the averages for the sympathetic groups (I-V) and the parasympathetic groups (VI to X) are shown. In these summaries, it will be noted that (1) the amount of serum calcium and potassium is increased in the sympathetic group, but the ratio remains unchanged, (2) the albumin-globulin ratio is lower in the sympathetic group, (3) the Kromayer time is somewhat prolonged, (4) the electrical resistance of the skin is higher, (5) the reactions to epinephrine (as computed mathematically) are, of course, higher in the sympathetic group, (6) the subjects are proportionally lighter in weight.

As there are relatively many nonreactive persons in each group, we have narrowed the selection of the material to the groups more strikingly different, and for this purpose have taken groups I, II and III for the sympathetic and groups VII and X for the parasympathetic types. These groups contain fifty and twenty-four persons, respectively.

In table 4B, it will be noted that the sympathetic group becomes more permeable, remains high in calcium and potassium content and retains the other differences previously noted. In addition, differences make their appearance in blood pressure, in the reaction to ice and in the red flare of the skin reactions.

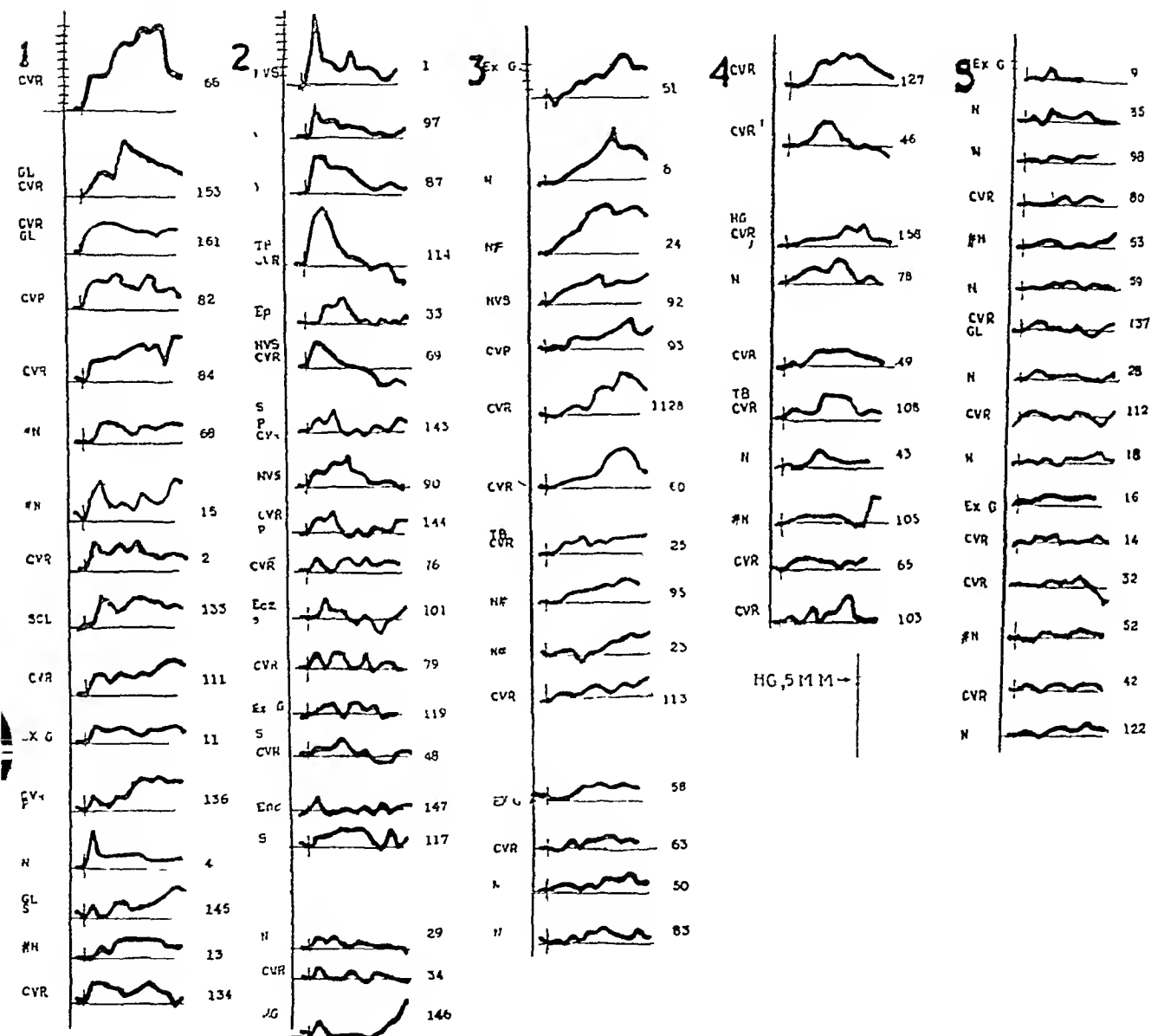


Fig 1—Graphic records of systolic blood pressure of sympathetic groups. Numbers at the right indicate the patient's number. The abbreviations at the left indicating diagnosis, represent the following: *N*, normal, *#N*, normal but roentgen-ray evidence of healed parenchymal tuberculosis, *CVR*, cardiovascular renal complication, *GL*, glaucoma, *Scl*, scleroderma, *Ex G*, exophthalmic goiter, *P*, pellagra, *S*, syphilis, *NVS*, nervous neuropsychasthenia, *TB*, tuberculosis, *Ep*, epilepsy, *Ecz*, eczema, *Enc*, encephalitis, *MG*, myasthenia gravis, *HG*, Hodgkin's disease, *Urt*, urticaria, *Ang Neu Ed*, angioneurotic edema, *HD*, heart disease, *NS*, normal, sensitized, *G*, glandular, feminine type, *Ca Thy*, carcinoma thyroid, *D*, dwarf, *F*, fever, bronchitis.

We can go one step farther and select ten of the outstanding cases of each series and examine their averages. The cases selected include the first ten of group I and the last ten of group VII. The averages are recorded in table 4.

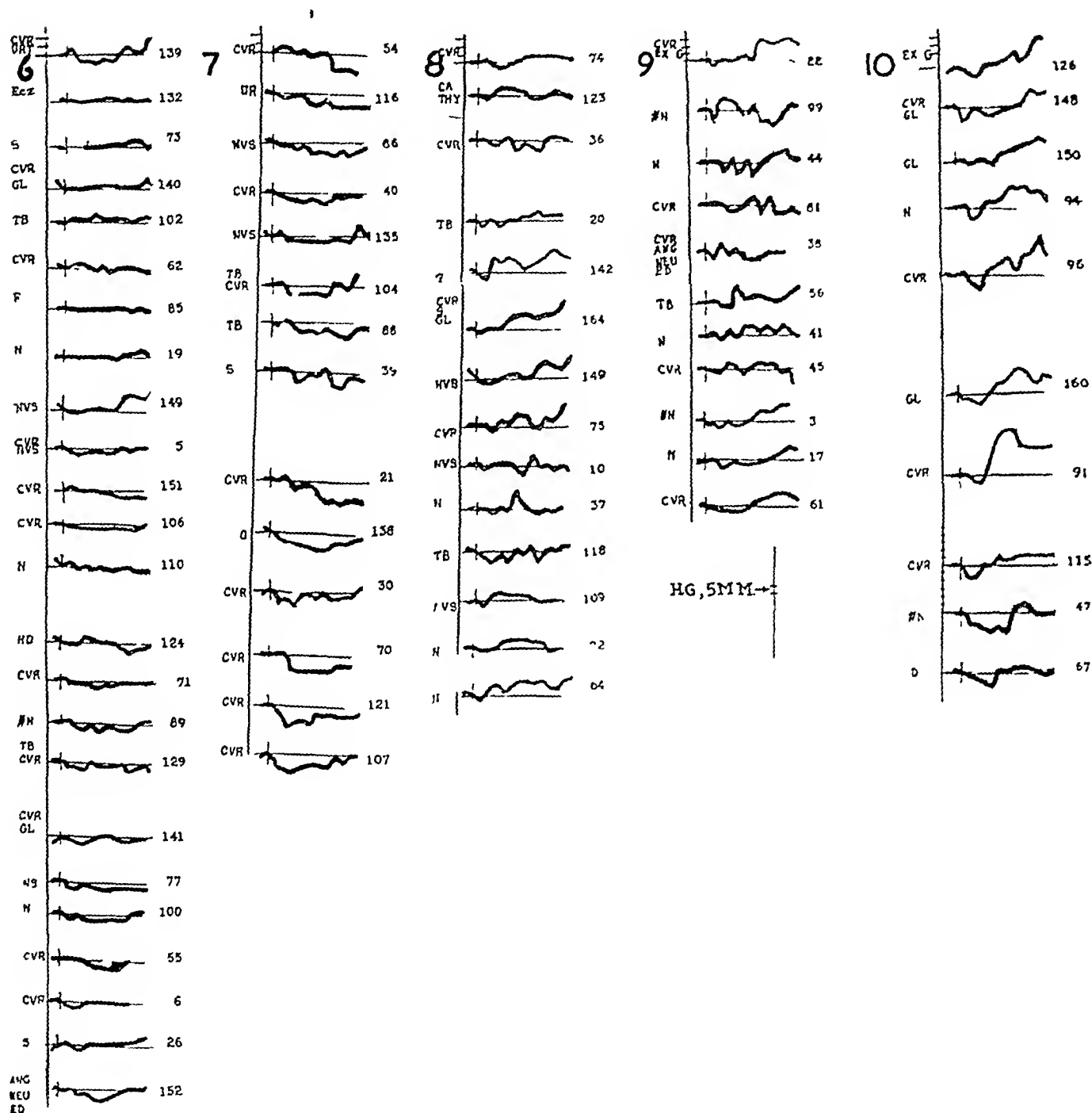


Fig 2—Graphic records of systolic blood pressure of 'parasympathetic groups'

We now have the outstanding group of contrasting persons and can note that the sympathetic group is characterized by (1) more permeable skin capillaries, (2) a higher amount of calcium, but a lower potassium calcium ratio, (3) a smaller proportion of albumin in the

TABLE 3—Average Results of Examinations Made on Individuals in Ten Groups¹

Number in Group	Group	Blister Time (a)	Permeability (a)	Inflammatory Index (a)	Calcium	Potassium	Potassium-Calcium Ratio	Sugar	Albumin/Globulin (b)	Kromayer Time (c)	Basal Metabolism	Skin Resistance (d)	Muscle Reaction (e)	Blood Pressure	Pulse Rate	Reaction to Epinephrine, P P (f)	Reaction to Epinephrine, P P x P R (g)	Carbon Dioxide	Reaction to Ice (h)	Age	Wt / Lt (i)	Cholesterol	Epinephrine, White	Epinephrine, Red	Morphine, White	Morphine, Red	Thyroxin, White	Thyroxin, Red	Caffeine, White	Caffeine, Red
16	1	5	4	8.7	10.6	18.8	1.8	71	2.1	1.8	86	0.13	1	120/70	78	22	25.5	55.5	21	15.5	161	202	20	10	11.6	10.8	14	4	21	2
16	2	8.8	63	8.8	9.7	20.2	1.8	72	1.9	2.3	73	0.55	1.8	127/63	78	14	25	57.7	18	42	2.6	216	10.2	8.6	11.4	13.1	11.6	3.6	18.4	1.8
16	3	7.3	66	9	10.2	22.7	2.2	77	1.5	2	8	0.39	2.5	122/67	76	25	36	57.8	19	11	215	223	20	8.8	10.8	16	13.2	5.4	16.6	2.4
10	4	8.3	61.5	8.4	9.86	17.1	1.74	67	2.25	2.3	121	0.41	1.5	113/67	76	20	31.2	58.1	15	17.9	207	206	19.6	9.4	11.8	11.2	13	6.4	19.2	2.8
10	5	9	65	10.1	10.5	20.5	1.67	71	2.1	1.75	13	0.42	3.4	125/66	75	19	19	57.1	16	37.5	193	220	20	8.8	11	16	11.1	9.4	16	2.8
12	6	7.3	19	6.5	10.3	20	1.97	62	2.2	1.83	65	0.16	2.3	110/67	78	5	6	58	21	40	217	204	19.2	8.6	11	11	12.4	4.1	18.8	3.1
14	7	7.8	63	9	10	19.9	1.99	73	2.1	1.75	9.7	0.16	2.1	133/66	77	3	6	57	22	17.7	227	201	20	8.8	10.2	13.9	9.4	8.2	19.2	1.8
11	8	8.1	66	8.6	9.5	18.8	1.86	76	2.5	1.96	9.6	0.16	3.6	127/70	76	7.5	19	57.3	14	12	206	226	19.6	9.6	12.8	12.1	10.8	5.2	16.8	3.1
11	9	6.5	61	10	10.1	19.9	1.97	74	2.1	1.76	11	0.25	1.6	130/75	71	12.1	23	6.1	16	12.1	23.0	210	20	8.6	12.4	16.1	11.2	4.8	16.1	1
10	10	10.1	58	4.4	9.3	19.6	2.08	71	2.2	1.58	19	0.25	1	131/71	69	9.6	15.5	59.7	16	35.7	213	227	18	8.6	10.98	9.1	13.6	5.2	23.2	1

* a, blister time—time in hours for formation of blister on forearm following erythroides plaster, permeability—ratio of protein in blister to protein in epillary blood, inflammatory index—permeability divided by blister time in hours, Petersen, Wm F, and Willis, D A Arch Int Med 663 (Nov) 1923 b, method of Rohrer (Deutsches Arch f Klin Med 124 221, 1916) c, time in hours of erythematous appearance of erythematous following a 30-second exposure of the forearm to Kromayer lamp d, resistance of skin of the forearm to passage of electric current e, muscle reaction (cathodic closing contraction) in milliamperes f, average increase or decrease in pulse pressure (in percentage of preinjection level) for one hour after injection g, average increase or decrease in pulse pressure times pulse rate (in percentage of preinjection level) for one hour after injection h, appearance time of erythema (in seconds) following transient application of ice to the chest wall i, weight in pounds divided by length in inches j, average size of wheal and flare (in mm) following intracutaneous injection of epinephrine, 1 1,000,000, 1 100,000, 1 10,000, 1 1,000, morphine, 1 10,000,000, 1 1,000,000, 1 100,000, 1 10,000, caffeine, 1 100

TABLE 4—*Averages for Sympathetic and Parasympathetic Groups*

	Blister Time	Permeability	Inflammatory Index	Calcium	Potassium	Potassium-Calcium Ratio	Sugar	Albumin-Globulin Ratio	Kromayer Time	Basal Metabolism	Skin Resistance	Muscle Reaction	Blood Pressure	Pulse Rate	P P Reaction to Epinephrine,	P P × P R Reaction to Epinephrine,	Carbon Dioxide	Reaction to Ice	Age	Weight-Length Ratio	Cholesterol	Epinephrine, White	Epinephrine, Red	Morphine, White	Morphine, Red	Thyroxin, White	Thyroxin, Red	Caffeine, White	Caffeine, Red
Sympathetic Group I-V																													
V	81	616	80	102	200	197	725	201	202	65	053	34	123/6	76	18	27	372	186	45	292	213	197	9	112	11	126	18	186	22
Parasympathetic Group VI-X																													
7	63	83	83	99	197	2	724	226	179	11	04	31	122/69	75	72	13	376	184	113	218	216	192	88	114	136	114	4	188	25
Sympathetic Group I, II, III																													
8	65	77	77	101	205	203	71	184	205	8	016	8	121/66	77	29	38	57	192	428	205	213	197	91	112	132	128	12	184	2
Parasympathetic Group VII and X																													
83	61	73	73	97	196	202	72	215	164	13	022	3	133/69	73	7	10	581	178	198	223	213	192	86	104	118	11	28	208	14
Average of Last Ten Persons, Group I—Outstanding Sympathetic Cases																													
(77	691	6	108	183	171	729	21	172	104	041	1	123/70	80	214	267	516	23	52	203	209	194	94	106	132	12	4	212	26
Average of Last Ten Persons, Group VII—Outstanding Parasympathetic Cases																													
77	645	83	94	94	193	204	71	234	195	109	043	2	110/75	80	-13	106	377	20	50	229	218	20	834	102	132	114	32	192	24

serum, (4) a more rapid reaction to the Kromayer lamp, (5) a more sluggish muscle reaction, (6) a lower blood pressure, (7) a lower carbon dioxide combining power, (8) a slightly longer time before reaction to ice occurs, (9) a lower weight-length ratio, and (10) apparently a slight diminution of the size of the morphine and thyroxin wheal in the parasympathetic groups and a somewhat less marked red flare in the reactions to epinephrine, morphine and thyroxin

It will also be noted that in the more outstanding cases (in sympathetic as well as in the parasympathetic group), the subjects are older than the average, and the pulse rate is higher, in neither group are there absolutely normal persons

RESULTS OF EXPERIMENTAL WORK

There seems little doubt that the permeability of the capillaries of the skin in the sympathetic group is increased. The ratio for twenty normal persons (38.3 years of age) was found to be 62. The ratio in the groups in which the reaction was sympathetic increased from 64.6 to 65 and finally to 69, as the more marked cases (table 4 A, B, C) were selected. This may have a direct relation to the activity of the thyroid gland, for we find⁵ that an increase in permeability is one of the outstanding phenomena of exophthalmic cases, a feature which is promptly influenced by thyroidectomy⁶

Interest during recent years has centered about the possible relation of the vascular response to epinephrine and the amount of calcium or potassium, or the potassium-calcium ratio. There seems little doubt concerning the general association of calcium with sympathetic effect. Thus injections of calcium chloride increase the blood sugar and make the urine acid, potassium salts have the opposite effect. Calcium increases the pressor effect of epinephrine, while potassium diminishes the effect. Kylan finds that in patients with the lower potassium-calcium quotients, the pressor effect of epinephrine is more marked. With quotients over two, almost every patient examined gave a vagotonic reaction. The literature is reviewed both by Kylan and by Zondek, so that we shall not discuss it at this time.⁷

In the examinations that we have recorded, it is first of all apparent that the entire sympathetic group has a somewhat higher calcium level,

5 Petersen, W. F. Arch Int Med 39:19 (Jan) 1927

6 Petersen, W. F., Seed, L., and Levinson, S. A. Arch Int Med, to be published

7 Our calcium values for normal subjects are 9.7, potassium, 20.3 the potassium-calcium ratio, 2.1

the difference between the sympathetic and parasympathetic groups increasing as the more marked cases are selected as shown in table 4

(a) Sympathetic	102		
Parasympathetic	99	Difference	03
(b) Sympathetic	101		
Parasympathetic	97	Difference	04
(c) Sympathetic	108		
Parasympathetic	96	Difference	12

The corresponding potassium averages and the potassium-calcium ratios are also shown in table 4

	Potassium	Potassium-Calcium Ratio
(a) Sympathetic	20	1.97
Parasympathetic	19.7	2
(b) Sympathetic	20.5	2.03
Parasympathetic	19.6	2.02
(c) Sympathetic	18.8	1.74
Parasympathetic	19.8	2.04

Only in the extreme cases of the "sympathetic" type is there an association of a low potassium-calcium ratio with the sympathetic effect, and in the individual cases there are many conflicting results. This can also be noted in the calcium, potassium and the potassium-calcium ratio for the first three groups in table 3, all of which are strongly sympathetic in reaction. Here the first group (immediate and persistent systolic rise) has a ratio of 1.8, the second group (immediate rise, followed by a fall) a ratio of 2.08, while the third group (slow but continuous rise) has a ratio of 2.22. It would be attractive to postulate that these differences in types of reaction are associated with the differences in the ionic balance, but we should be hesitant in drawing such a conclusion for the following reasons:

The calcium (and potassium) of the serum may reach an identical level under diverse physiologic states of the tissue. There may be a hypercalcemia when calcium is leaving the tissues and increasing in the serum. On the other hand, a hypercalcemia may exist when there is a current in the opposite direction when calcium excess is being offered the body, and when both the serum and the tissues may consequently be saturated. Under such conditions the reactions of the tissue cells may be diametrically opposite but the calcium level is the same in both instances. Similar conditions may hold for the potassium level. We have discussed the constant shifting of the calcium and potassium values as observed in previous experimental infections.⁸ We must further

⁸ Petersen, W. F., Muller, E. F., and Milles, G. *Ztschr. f. d. ges. exper. Med.* 60: 336, 1928.

keep in mind that the ionic effect of the calcium may be quite different from that indicated by the total calcium concentration

It is curious that there is practically no difference in the levels of the sugar content of the respective groups. We might anticipate that the sugar level of the sympathetic series would be higher. This in itself is, we believe, additional proof that the concept of a uniform sympathetic orientation of the individual does not exist. These patients may have a greater response of their vascular musculature, but the hepatic sugar mechanism has not been altered.

There is evident throughout a lesser amount of globulin in the parasympathetic series. Table 4 shows the following $\frac{\text{albumin}}{\text{globulin}}$ ratio in the three series:

(a) Sympathetic	2.01
Parasympathetic	2.26
(b) Sympathetic	1.84
Parasympathetic	2.15
(c) Sympathetic	2.1
Parasympathetic	2.34

The normal ratio is around 2.22

The averages for the appearance time of the erythema following irradiation by the Kromayer lamp are conflicting. The averages for the larger groupings, 4 A and B, indicate that the sympathetic groups are somewhat less responsive, the figures being:

(a) Sympathetic	2 hours
Parasympathetic	1.8 hours
(b) Sympathetic	2.05 hours
Parasympathetic	1.64 hours

When the most marked groups are taken into consideration, the figures are:

(c) Sympathetic	1.6 hours
Parasympathetic	1.7 hours

indicating merely that the response is in general more rapid in both groups than in the normal person.

Practically no differences exist in the basal metabolic rates for the two groups.

The sympathetic group has in general a higher skin resistance (electrical), but when the most marked group (C) is examined, this difference is not found.

A distinct difference seems to make its appearance in the electrical reactivity of the muscles. This is apparent if one compares the normal

reaction of the muscles—3.7 milliamperes (cathodal closing contraction) to the group averages as shown in table 4

(a) Sympathetic	3.4 ma
Parasympathetic	3.1 ma
(b) Sympathetic	3.8 ma
Parasympathetic	3 ma
(c) Sympathetic	4 ma
Parasympathetic	2.3 ma

As the parasympathetic group is in general inclined toward alkalosis, the increased muscular irritability evident in the group is in accord with the difference in carbon dioxide combining power.

The blood pressure, as might be anticipated from the known effect of epinephrine on the average hypertonic case, shows a distinct increase for the parasympathetic groups, as shown in table 4.

(a) Sympathetic	123/66
Parasympathetic	122/69
(b) Sympathetic	121/66
Parasympathetic	133/69
(c) Sympathetic	123/70
Parasympathetic	140/75

The pulse rate increases in the final group, in which the most abnormal persons are included. There is no appreciable difference between the sympathetic and parasympathetic groups.

The most marked (C) group would indicate a lower carbon dioxide combining power for the sympathetic group. This is indicated in group (B) as well, while the figures for the larger series (A) reveal no differences. It is generally assumed that the sympathetic status involves acidosis.

The reactivity of the capillaries to ice seems somewhat lessened in the persons in the sympathetic group. While the response of those in the large group (A) is alike, the (B) grouping indicates a difference of 1.4 seconds, and in the (C) grouping this is increased to three seconds. The general slowing up of the reaction from A to C is probably associated with the advancing age, which increases from an average of 45 to 51 years.

The difference between the two groups apparent in the weight-length ratio begins in the A group and progresses, the differences being 0.16, 0.18 and 0.23 in the three groups. This difference seems to be quite conclusive.

It is generally assumed⁹ that cholesterol differences are of some importance in constitutional differentiation. Our figures fail to reveal any striking changes in the groups examined.

⁹ Mjassnikow. Ztschr. f. klin. Med. **105**: 228, 1927.

The individual reactions of the various pharmacologic agents used for the skin reactions show considerable latitude, particularly in the case of the red flare that appears in response to thyroxin and caffeine, so the results must be interpreted with considerable caution

COMMENT AND SUMMARY

If we now seek to interpret our observations, we must consider them in terms of the normal and perhaps compare them to observations made

TABLE 5—*Results for Normal Persons and for Sympathetic and Parasympathetic Cases and Cases of Exophthalmic Goiter*

	Normal Persons	Parasympathetics Table 4 C	Sympathetics Table 4 C	Exophthalmic Goiter
Number in group	20	10	10	12
Blister time	6.8	7.7	7.7	5.4
Permeability	62	64.5	60	72
Inflammatory index	9.3	8.3	9	13.3
Calcium	9.7	9.64	10.8	10.5
Potassium	20.3	19.83	18.83	21.1
Potassium Calcium ratio	2.1	2.04	1.74	2.03
Sugar	72.8	71	72.6	88
Albumin globulin ratio	2.22	2.34	2.1	1.79
Kromeyer time (minutes)	110	117	103	103
Basal metabolism	+5	10.9	10.4	48
Skin resistance	0.33	0.43	0.41	0.23
Muscle retention	3.7	2.3	4	2.8
Carbon dioxide combining power	57.6	57.7	54.6	54.2
Blood pressure	116/70	140/75	123/70	140/70
Pulse pressure	46	65	53	70
Pulse rate	68	80	80	102
Reaction to epinephrine				
P.P. in per cent	19.6	-1.3	21.4	19
P.P. × P.R. in per cent	28.6	0.6	26.7	33.7
Reaction to ice	14.5	20	23	10
Weight-length ratio	224	229	231	201
Cholesterol	222	218	209	203
Epinephrine wheal (mm.)	21	20	19.4	16
Epinephrine flare (mm.)	9.36	8.34	9.4	10.6
Morphine wheal (mm.)	11.7	10.2	10.6	11.4
Morphine flare (mm.)	16.3	13.2	13.2	11.6
Thyroxin wheal (mm.)	11.6	11.4	12	10.4
Thyroxin flare (mm.)	5.45	3.2	4	4.6
Caffein wheal (mm.)	17.9	19.2	21	15.2
Caffein flare (mm.)	3	2.4	2.6	1
Age	40.2	50	50	39

in a disease condition in which sympathetic overbalance has been frequently suggested, mainly that of exophthalmic goiter. We have tabulated the most important results for normal persons, for our outstandingly contrasting sympathetic and parasympathetic cases, and for cases of exophthalmic goiter.¹⁰

¹⁰ Exophthalmic goiter by no means represents a purely sympathetic overbalance, the autonomic manifestations are obviously mixed in character (Eason, J. Exophthalmic Goiter, Edinburgh, Oliver & Boyd, 1927)

Thus it becomes apparent that the sympathetic group approaches the exophthalmic goiter in permeability, in high calcium concentration, in shortening of the Kromayer time, in relative acidity, in response to epinephrine, in weight-length ratio and in relatively low cholesterol content. This group approaches the parasympathetic group, on the other hand, in the electrical response, as well as in the higher systolic blood pressure.

Chart 3 illustrates the relative skin reactions noted in table 4.

An analysis of the reaction to epinephrine has been made on 100 so-called normal persons, as well as on about fifty patients. In contrast-

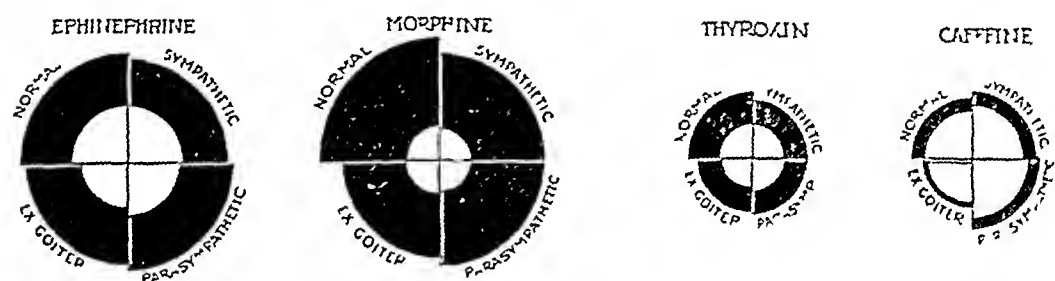


Fig. 3—Average wheal (white) and flare (black) following intracutaneous injection of epinephrine, morphine, thyroxin and caffeine into normal persons, patients with exophthalmic goiter and the sympathetic and parasympathetic "groups" (4 C)

ing the outstanding sympathicotonic cases with the outstanding vagotonic cases, the averages indicate that the sympathicotonic group differs in that the members of the group have more permeable skin capillaries, a lower potassium-calcium ratio, more globulin, a lower carbon dioxide combining power and a lessened muscular electrical reactivity. The persons weigh less and have a lower blood pressure.

Comparative data are also presented for twenty normal persons, twelve patients with exophthalmic goiter and the most marked sympathicotonic and vagotonic types.

PANCREATIC FUNCTION

I THE QUANTITATIVE ESTIMATION OF PANCREATIC SECRETION *

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The value of the quantitative estimation of pancreatic function is apparent. Interest in pancreatic function really goes back to the time when Einhorn introduced the duodenal tube¹. Previous to that time, pancreatic functional tests depended on examinations of the feces, which were inaccurate. In these examinations, when many striated muscle fibers, steatorrhea and fatty acid crystals are found, there is generally pronounced dysfunction of the pancreas. Other conditions than pancreatic disease may give positive observations, and often, in distinct pancreatic involvement, the feces tests yield normal reactions, owing to the fact that the enzyme activity of intestinal bacteria has supplanted deficient pancreatic secretion. The Schmidt test,² Kashiwado's modification³ and Einhorn's bead test⁴ show also only extreme dysfunction of the pancreas in cases in which the observations are positive. The tests of enzymatic activity in feces as suggested by Gross⁵ are also more or less inaccurate, probably more often inaccurate than accurate. The oil regurgitation method of Boldyreff⁶ and Volhard⁷ is not practical. A

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1 Einhorn, Max. Ueber Gewinnung von Duodenalinhalt beim Menschen, *Berl. klin. Wchnschr.* **47** 522, 1910.

2 Schmidt, A. Die klinische Bedeutung der Ausscheidung von Fleischresten mit dem Stuhlgang, *Deutsche med. Wchnschr.* **25** 811, 1899.

3 Kashiwado, T. Ein Beitrag zur Kernverduung und eine Vereinfachung der Schmidt'schen Kernprobe zur Erkennung von Pancreasachvie, *Deutsches Arch. f. klin. Med.* **104** 584, 1911.

4 Einhorn, Max, cited by Aaron, C. D. *Diseases of the Digestive Organs*, 1921, p. 129.

5 Gross, O. Zur Funktionsprufung des Pankreas, *Deutsche med. Wchnschr.* **35** 706, 1909.

6 Boldyreff, W. Der Uebertritt des natuerlichen Gemisches aus Pankreassaft, Darmsaft und Galle in den Magen, *Arch. f. d. ges. Physiol.* **121** 13, 1907.

7 Volhard, F. Ueber die Untersuchung des Pankreassaftes beim Menschen und eine Methode der quantitativen Trypsinbestimmung, *Munchen med. Wchnschr.* **54** 403, 1907.

series of methods was devised in which the duodenal tube was used and in which the three ferments of the duodenal contents were estimated. Objections were made that the duodenal contents while the patient is fasting often show low enzymatic activity or that the amount is too scanty to permit satisfactory analysis, notwithstanding the fact that the pancreas is not involved. Several stimulants for pancreatic secretion, such as bouillon, hydrochloric acid, ether, cream and peptone, thus were applied by various workers. After an injection of these stimulants through the tube into the duodenum, the duodenal return was aspirated at an arbitrary period, and the enzymatic activity was estimated. Criticism of any of the pancreatic quantitative tests is common, however, on the basis that a quantitative test of pancreatic enzymes could not be accurately carried out. It was pointed out that the presence of a considerable amount of saliva, gastric juice and biliary secretion so diluted the duodenal contents that an accurate quantitative study of the pancreatic ferments could not be made. In reality, on the one hand, great enzymatic activity is sometimes detected when the pancreatic secretion is scanty, while, on the other, little activity is encountered when the secretion is profuse, as the consequence of dilution with the previously mentioned fluids. This shows that the methods hitherto applied as quantitative tests encounter theoretical as well as real objections. We have carefully considered this point and have devised a method which enables one to make a reliable and accurate estimation of the pancreatic function.

METHOD

Early in the morning when the stomach is empty, the tip of a duodenal tube is passed into the duodenum, and the position of the tip is verified by fluoroscopic examination. After some experience it is usually recognized without fluoroscopic examination that the tip lies in the duodenum. The tip of the tube usually is found at the lowest part of the second portion of the duodenum. When the tip of the tube is found at the bottom of the stomach, it can often be manually pressed from the stomach into the duodenum under fluoroscopic inspection. After passing through the pylorus, the tip usually proceeds quickly to the lowest part of the second portion of the duodenum and stays there almost permanently, so that it is found at almost the same place before and after three hours collection of the duodenal contents. The duodenal contents are collected under constant suction by means of a syringe. For this purpose, it is important that the metal tip of the tube be provided with a wide hole at the top (3.5 mm or more in diameter) and many small holes at the side wall, otherwise the holes can easily be filled by mucous clots. Suction of the duodenal contents is performed under a condition of fasting, or several kinds of stimulants are injected through the tube into the duodenum and five minutes allowed for them to pass beyond the duodenum, then the duodenal return is aspirated by suction with a syringe. Sulphuric ether (usually 3 cc), 10 per cent alcohol (30 cc) distilled water (30 cc), 0.2 per cent hydrochloric acid (30 cc) etc., are used as stimulants. The outflow of the duodenal return is usually copious at first after the injection of the stimulants but the amount as well as the enzymatic activity

varies greatly in a short period not only in different but also in the same persons. In fractional collections, the fluctuation of the enzymatic activity is especially obvious. Owing to the presence of a considerable amount of saliva, gastric juice and biliary secretion, the duodenal contents are so diluted that a quantitative study of the pancreatic ferments is not accurate unless the amount of the fluids is taken into consideration. The vital point of our method consists in the multiplication of the degree of enzymatic activity by the amount of the duodenal return in cubic centimeters in exactly fixed time, the product of the multiplication is then expressed in units of pancreatic enzyme efficiency. It is most important, however, to know what proportion of the secreted fluids into the duodenum might be secured by suction. To solve this question two duodenal tubes are tied together so that the one tip follows the other. After it is ascertained that both tips lie in the duodenum, a measured portion of water with phenolphthalein (to 100 cc of distilled water is added 1 cc of 1 per cent alcoholic solution of phenolphthalein) is passed through one tube into the duodenum, and the return is collected by another with constant suction. After the original solution as well as the duodenal return is alkalinized and when the color is completely developed, the color is measured with the Duboscq colorimeter, and the amount of fluid

TABLE 1—*Results Obtained in Constant Suction Method of Recovery of Duodenal Contents*

Number	Amount of Poured Solution, Cc	Amount of Duodenal Return, Cc	Calculated Amount of Recovered Fluid, Cc	Bile Pigment (Meulengraekt)	Recovered Amount, per Cent
1	22	21.8	21.1	48×	96
2	22	26.3	21.7	22×	98
3	22	21.8	20.6	19×	94
4	22	21.2	21.9	43×	99

recovered is calculated. When the duodenal return is stained distinctly with bile, the color changes after alkalinizing, so that it is necessary also to add a portion of bile to the original solution to obtain the same color and to make it favorable for comparison.

The results in table 1 show that from 94 to 99 per cent of the solution poured into the duodenum can be recovered by constant suction, indicating that the method is reliable for the quantitative collection of the duodenal contents.

The amount of the duodenal contents aspirated in a short period, as well as the degree of enzymatic activity, varies greatly whether stimulants are used or not, an hour's collection is also variable, a two hours' collection is somewhat compensating, and a three hours' collection is much more reliable and gives consistent results. To make more than a three hours' collection is not practical and is inconvenient for both the patient and the examiner. Therefore, we choose the three hour method. The enzyme activity is estimated at every hour or every half hour period and summed up.

As the test of enzymatic activity we apply the Gross casein method⁸ for trypsin, Okada's colorimetric method⁹ for amylase and Rona-Michaelis' tributyrin

8 Gross, O. Die Wirksamkeit des Trypsins und eine einfache Methode zu ihrer Bestimmung, Arch f exper Path u Pharmacol 58 157, 1906

9 Okada, S, unpublished

method¹⁰ for lipase, each with some modifications. The entire procedure is as follows

Estimation of Trypsin—The reagents are (a) casein solution—0.1 Gm of casein *Rhenania* and 0.1 Gm of sodium bicarbonate are dissolved in distilled water by heating under constant stirring and after cooling brought to exactly 100 cc, (b) phosphate mixture—hundredth molar primary sodium phosphate, fiftieth molar secondary sodium phosphate and 8.5 Gm of sodium chloride are dissolved in distilled water and made up to exactly 1,000 cc, the p_H of this solution is 7.8, (c) acetic acid, alcohol solution—50 cc of absolute alcohol, 2 cc of glacial acetic acid and distilled water up to 100 cc

The procedure is as follows. The duodenal fractions are diluted usually 100 times with a phosphate mixture. Into the six tubes (10.5 by 1.2 cm), in a rack, one should accurately pipet in succession, 1, 0.63, 0.4, 0.25, 0.16, 0.1 cc of the 100 times diluted duodenal return and make up all tubes to 1 cc with phosphate mixture. Then the tubes are placed in a water bath at 38 C. As soon as the contents of the tubes have been brought to this temperature, 2 cc of a 0.1 per cent solution of casein is added to each tube, the contents are mixed, and incubation is then carried out for exactly thirty minutes at 38 C. After the incubation has been completed, 10 drops of a solution of acetic acid and alcohol are at once added to each tube, and one should watch to see in which tubes no trace of turbidity appears when the tubes are not stirred. The last tube in the row in which turbidity appears shows that digestion is complete, and this tube is used for the calculation of enzymatic activity. Thus, is obtained the enzymatic activity of 200, 320, 500, 800, 1,250 and 2,000 units. When this activity is low, 1 cc of casein solution is used, or the duodenal return is diluted to ten times or less. To show the total enzymatic efficiency, we often use kilo-units. By 1 kilo-unit of trypsin is meant the enzymatic activity when 1 Gm of casein is completely digested in thirty minutes.

Estimation of Amylase—The reagents are (a) starch solution—1 Gm of soluble starch (Merck) is dissolved in distilled water by heating until there is exactly 100 cc after cooling, (b) dextrose solution—0.1 Gm of anhydrous and extra pure grape sugar (Merck) is dissolved in distilled water, and the volume is brought to exactly 100 cc, (c) 20 per cent sodium carbonate solution—20 Gm of sodium carbonate is dissolved in distilled water until 100 cc is produced.

The procedure is as follows. Three tubes (16.5 by 1.8 cm) are placed in a rack. Nine cubic centimeters of starch solution are accurately pipetted to the first tube, 9 cc of starch solution and 1 cc of distilled water to the second tube (control tube) and 10 cc of dextrose solution to the third tube. Then the tubes are placed in a water bath at 38 C. As soon as the contents of the tubes have been brought to this temperature, 1 cc of the 100 times diluted duodenal return (same dilution as used in the estimation of trypsin) is added to the first tube, the content is mixed, and incubation is then carried out for exactly fifteen minutes at 38 C. After the incubation has been completed, about 0.3 Gm of dry trinitrophenol is at once added to the three tubes and thoroughly stirred, and each is filtered into a dry test tube through a folded filter paper. Five cubic centimeters of the filtrate is pipetted into a test tube, 1 cc of a 20 per cent solution of sodium carbonate is added and the solution is thoroughly mixed and then placed in a

10 Rona, P., and Michaelis, L. Ueber Ester-und Fettspaltung im Blute und im Serum, *Biochem Ztschr* 31:345, 1911. Willstätter, R., and Memmen, F. Zur stalagmometrischen Bestimmung der lipatischen Tributyrinhydrolyse, *Ztschr f physiol Chem* 129 1, 1923.

boiling water bath for fifteen minutes. At this stage, the color is completely developed, though uninfluenced, by prolonged heating. The solution is then cooled to room temperature, and water is added to bring the volume of the first tube up to from 30 to 100 cc, according to the depth of the color. The volume of the second tube is usually brought up to 30 cc, and that of the third tube to 50 cc. The solution is thoroughly mixed and compared in the Duboscq colorimeter, the solution of the third tube being used as standard. Duplicate tests are desirable. When the duodenal return is diluted 100 times, the units of amylase in 1 cc, for instance, are

	Diluted up to cc	Colorimetric reading mm
Tube 1 (main)	70	18.0
Tube 2 (control)	30	17.8
Tube 3 (dextrose)	50	20.0

Then the main tube contains sugar when incubation is finished,

$$10 \times \frac{20}{18} \times \frac{70}{50} = 15.56 \text{ mg}$$

and the control tube contains sugar

$$10 \times \frac{20.0}{17.8} \times \frac{30}{50} = 6.74 \text{ mg}$$

Therefore, the difference is 8.82 mg, which is produced by 1 cc of 100 times diluted duodenal return in fifteen minutes. Consequently, 1 cc of the original duodenal return can produce sugar from soluble starch to the amount of 882 mg in fifteen minutes, and the degree of the amylolytic activity of this duodenal return is 882. We also often use kilo-units. By 1 kilo-unit is meant the enzymatic activity in the production of 1 Gm of sugar from soluble starch in fifteen minutes.

Estimation of Lipase—The reagents are (a) saturated tributyrin solution—1 drop of tributyrin (Kahlbaum) is added to 100 cc of distilled water and thoroughly shaken, left for a day at room temperature and then filtered through wet filter paper, (b) regulating solution—19 parts of third molecular secondary sodium phosphate ($\text{Na}_2\text{HPO}_4 + 12\text{H}_2\text{O}$) and 1 part of third molecular primary potassium phosphate (KH_2PO_4) are mixed, the p_{H} of this mixture is 7.8, (c) adequately diluted duodenal return—to 1 cc of the duodenal return is added from 1 to 2 drops of blood serum following the procedure of K. Gyotoku to make the enzyme activity tenable, then it is diluted usually from 100 to 1,000 times with glycerol, which has previously been diluted with an equal part of 1 per cent ammonium phosphate, several provisional determinations being made until 1 cc of the diluted solution contains about 1 unit of enzyme.

The procedure is as follows. To 1 cc of diluted duodenal return is added 2 cc of phosphate mixture and 57 cc of saturated tributyrin solution, and an estimation is made every fifteen minutes for one hour, using Rona-Michaelis' drop-pipet. With this drop-pipet distilled water is measured, it counts seventy-seven drops at from 20 to 23 C, with an increase of approximately two drops for every 10 degrees of rising temperature and a decrease of one drop for every 10 degrees of falling temperature. When the saturated tributyrin is measured, the number of the drops is 116 at from 20 to 23 C, with an increase of approximately three drops for every 10 degrees of rising temperature and a

decrease of one drop for every 10 degrees of falling temperature. From four estimations a curve is produced, and the number of drops at fifty minutes is calculated. By 1 unit of lipase is meant an enzymatic activity when the decrease in the number of the drops is twenty in fifty minutes, i. e., about half the difference between saturated tributyrin solution and pure water.

Estimation of Bile Pigment—Meulengracht's bilirubin colorimeter for blood serum is used. One tenth gram of potassium bichromate is dissolved in 1 000 cc of distilled water and two drops of dilute sulphuric acid is added. A glass tube, 1 cm in diameter, is filled with this solution, closely stoppered and used as standard, 1 cc of the duodenal return is pipetted in a graduated glass tube of the same diameter as the standard tube and diluted with physiologic sodium chloride solution till it matches the color of the solution in the standard tube. The depth of the color of the standard solution is checked with pure bilirubin solution in chloroform and found to correspond with a 700,000 times dilution of this.

All the patients used in the experiments were adults who had been under careful observation in the hospital. Most of them showed only mild clinical symptoms, such as constipation and neurasthenia, and were thought to be free from pancreatic involvement. The data mentioned here, therefore, might be regarded as having been obtained in normal persons.

RESULTS

In general, the secretion is profuse immediately after the injection of the stimulants into the duodenum, so that the total enzyme efficiency is usually high in the first hour, but this is not always the case. The outflow of the duodenal return usually is intermittent or rhythmic, even when the secretion is profuse. Sometimes there is an interval of more than thirty or sixty minutes in which no trace of secretion is seen, resulting again in a profuse secretion. When the outflow is collected fractionally every thirty minutes, the fluctuation is obvious, a fact which shows that the data obtained during short periods give but little information as to pancreatic activity. It is necessary to adopt the suction to the progress of the secretion and not to give much power when there is no secretion, otherwise, it is likely to injure the duodenal wall and even cause leakage of the blood. Disagreeable by-effects, such as burning pain of the epigastrium, paleness of the face, syncope and headache are often encountered when ether is injected into the duodenum, but they are of short duration. Alcohol also causes drunkenness in some patients. Hydrochloric acid and water do not cause any by-effects. No direct relation exists between the depth of the color of the duodenal return and the concentration of the enzyme, though high enzymatic activity is usually encountered when the fluid is deep colored. Sometimes a colorless fluid is encountered when there is a relatively high degree of enzymatic activity (for example, in K. H. [table 2]) the fraction of the duodenal return from thirty minutes to one hour after the injection of 30 cc of

TABLE 2—Data of Observations in Survey

Name	Sex*	Age	Date	Stimu- lants Intro- duced Into the Duodenum	Amount of Duodenal Return in 3 Hours, Cc	Degree of Enzymatic Activity												Amyl- ase in 3 Hours, Kilo- Units	Trypsin in 3 Hours, Kilo- Units	Lipase in 3 Hours, Kilo- Units	Bile Pig- ment in 3 Hours, Mg	Gastric Juice	
						Trypsin			Amylase			Lipase											
						First Hour, Units	Second Hour, Units	Third Hour, Units	First Hour, Units	Second Hour, Units	Third Hour, Units	First Hour, Units	Second Hour, Units	Third Hour, Units	Free in Hydro- chloric Acid	Total Acidity							
S H	♂	22	1/12/27	No	125 0	500	800	800	1,177	908	1,401	1,520	1,330	2,910	95.2	131.8	238.8	21.2	61	83			
K H	♀	18	1/12/27	No	60.5	800	800	1,230	867	1,740	1,411	520	310	2,720	32.6	73.6	454.1	3.3	43	65			
A H	♂	34	1/12/27	No	91 0	800	800	800	1,301	594	1,215	990	310	1,720	71.0	113.9	119.0	14.6	13	28			
S S	♀	22	1/16/27	No	111 0	500	500	500	635	533	871	330	1,410	300	55.5	74.1	92.1	5.4	57	79			
K Y	♂	40	1/16/27	No	123.5	700	800	800	1,032	844	1,610	470	230	1,900	70.0	82.8	154.7	20.8					
S M	♂	28	1/22/27	No	119 0	500	500	500	1,418	1,177	1,057	270	690	1,032	59.5	145.1	73.7	13.9					
R K	♂	54	2/ 5/27	No	91.5	320	500	500	1,191	1,075	1,095	428	680	1,130	35.5	111.4	73.5	19.0	49	63			
E T	♀	20	2/ 5/27	No	174 0	300	320	320	1,072	743	929	600	810	992	69.8	165.8	184.2	13.8	30	51			
K A	♂	38	2/15/27	No	90 0	500	500	500	2,056	2,139	2,137	384	1,175	410	56.7	100.3	63.8	10.5					
W N	♂	19	2/15/27	No	12 0	800	800	800	2,108	2,076	1,938	272	1,180	1,821	27.8	85.9	41.5	3.4	41	61			
B K	♂	31	2/15/27	No	181 0	500	500	800	1,760	1,692	1,858	1,372	910	5,980	130.4	321.0	483.3	29.8	53	74			
T M	♂	37	2/25/27	No	123.8	320	800	800	1,984	2,571	2,652	238	17	190	69.9	290.6	22.8	9.5					
B K	♂	25	2/26/27	No	121 0	500	500	500	1,454	1,297	1,469	2,940	1,768	1,501	76.1	167.6	263.2	18.7	21	32			
L S	♀	27	3/ 5/27	No	10 0	1,250	200	200	2,415	1,540	1,391	2,880	830	2,080	49.7	79.1	100.5	8.9	20	42			
S T	♂	20	3/11/27	No	204 0	500	500	500	1,564	1,245	1,647	1,910	500	1,100	111.9	293.7	282.2	7.9					
K A	♂	16	5/ 7/27	No	105 0	500	500	500	1,733	1,018	1,515	832	1,596	2,500	96.9	267.8	38.7	6.8	41	46			
M N	♂	62	10/12/27	No	167 0	500	500	1,250	1,862	2,674	3,323	182	100	720	55.6	262.9	51.9	3.4	20	30			
S N	♂	38	10/27/26	Alcohol	90 3	500	320	635	1,020	1,897	2,432	1,703	600	510	62.0	55.7	113.9	20.0	30	48			
A T	♂	27	10/28/26	Alcohol	107 3	2,000	1,250	1,250	872	662	1,312	2,752	1,200	960	113.7	97.6	204.7	9.3					
K A	♂	49	11/ 2/26	Alcohol	107.8	300	800	800	1,222	938	803	1,518	855	1,050	71.1	134.1	108.2	4.0	35	48			
K Y	♀	51	11/ 9/26	Alcohol	90 0	500	320	700	1,157	995	1,081	1,225	625	625	19.4	58.5	32.6	3.8	39	51			
H K	♀	51	11/ 9/26	Alcohol	119.5	800	100	920	630	126	186	155	284	284	37.9	166.2	74.5	7.8	27	39			
S M	♂	29	11/16/26	Alcohol	123.5	500	800	800	1,620	1,638	810	232	120	136	112.5	112.4	211.9	17.0	57	77			
O I	♀	46	11/26/26	Alcohol	48.4	2,000	200	1,250	1,284	1,214	997	1,850	2,000	1,600	32.8	57.4	92.5	34.6	12	36			
					320	1,308	136	136	1,308	1,308	204	3,600	322	208									

K Y	♀	30	11/30/26	Alcohol	106 0	500	320	522	647	1,314	1,100	840	590	54 8	91 7	173 1	11 5	63	85
S K	♂	24	12/ 1/26	Alcohol	103 0	500	500	1,002	783	1,090	2,000	524	2,540	43 8	101 8	149 3	20 7	22	45
S T	♀	20	12/ 8/26	Alcohol	89 0	200	320	1,495	2,209	1,315	2,080	1,488	1,820	52 6	33 1	77 6	6 1	26	50
B E	♂	22	12/ 8/26	Alcohol	130 3	320	500	653	410	617	550	420	1,368	86 3	88 1	119 6	17 5	9	26
M S	♂	32	12/21/26	Alcohol	93 0	500	320	749	733	709	495	300	480	107 7	122 7	161 1	4 6	26	43
K H	♀	18	12/24/26	Alcohol	53 5	1,250	1,250	1,531	1,502	1,135	2,168	2,120	2,100	49 3	84 7	101 0	5 2	43	65
A H	♂	34	1/15/27	Alcohol	83 0	500	500	1,003	1,172	2,385	1,560	1,560	1,560	58 8	93 6	45 0	11 4	13	28
I T	♂	20	1/19/27	Alcohol	131 5	500	500	763	738	1,075	1,125	520	1,180	65 8	109 4	125 3	8 2	30	51
R K	♂	34	1/21/27	Alcohol	277 0	500	200	597	124	842	925	256	920	119 3	153 4	213 0	61 7	49	63
A T	♂	27	1/20/23	Ether	106 0	500	320	1,244	1,025	1,050	2,450	850		65 2	107 9	200 3	35 5		
K Y	♀	30	12/14/26	Ether	111 0	320	500	1,125	739	1,050	1,050	1,140		41 1	67 2	112 5	6 9	39	51
R E	♂	22	12/11/26	Ether	142 0	500	300	857	1,505	1,456	792	264	765	124 8	187 3	84 3	14 7	9	26
S K	♂	24	12/15/26	Ether	120 0	500	500	1,249	1,569	1,404	495	300	450	53 0	121 0	183 7	12 8	22	45
K Y	♂	40	2/ 1/27	Ether	65 0	200	500	1,878	1,236	1,264	723	200	1,504	37 2	93 9	96 3	21 1	51	104
S M	♂	28	2/ 2/27	Ether	166 5	100	500	1,215	1,359	1,629	1,200	350	2,620	37 8	130 0	73 1	13 0	42	59
L T	♂	20	3/23/27	Ether	231 0	320	500	935	1,050	1,035	1,120	512	1,590	93 0	230 0	326 1	28 1	30	51
K H	♀	18	1/10/27	Water	108 3	250	320	1,196	1,304	1,326	488	271	1,750	33 0	125 6	111 2	2 5	43	65
K Y	♀	40	1/21/27	Water	221 0	400	500	922	1,208	1,208	228		1,000	103 7	182 1	345 4	47 8	81	104
F K	♀	10	1/25/27	Water	181 8	320	500	781	1,239	635	1,510	880	2,050	78 4	187 6	97 3	11 6		
S Y	♂	20	10/13/27	Water	115 5	250	320	860	1,082	1,304	456	496	640	12 8	206 1	119 0	13 1	28	78
L T	♂	29	10/15/27	Water	88 0	20	500	1,887	1,401	1,120	870	1,120	1,110	44 1	197 5	32 7	2 6	25	37
S H	♂	22	1/ 6/27	Hydro	189 5	500	300	1,997	2,589	2,281	365	350	350	107 5	102 0	170 5	19 3	61	83
A H	♂	44	1/18/27	chloric acid	160 0	500	800	876	355	873	630	594	1,104	107 9	161 5	234 9	21 3	13	25
S S	♀	22	1/18/27	chloric acid	182 0	320	500	893	1,064	1,123	1,230	1,520	1,760	63 0	111 3	192 8	8 3	57	79
I T	♂	20	3/20/27	chloric acid	175 0	320	500	794	1,819	1,232	1,225	976	1,350	97 8	221 1	262 5	16 4	29	51
I T	♂	29	10/12/27	chloric acid	146 1	160	250	1,510	1,579	1,614	720	2,160	2,450	51 7	270 3	119 0	12 3	25	37

* In this column ♂ indicates male ♀, female
 † Two degrees of enzymatic activity are tabulated in cases in which collections were estimated separately every half hour
 ‡ The acidity of gastric juice is shown in one hour specimens after the Lawd Bo is test breakfast, though in most cases fraction of tests were made

distilled water into the duodenum was amount of the fluid, 29 cc , degree of trypsin, 400 , degree of amylase, 922, and degree of lipase, 228) A slight or nearly absent enzymatic activity and a great concentration of bile pigment are usually pathologic The stimulating power of ether on the pancreatic secretion, as suggested by Katsch and Friedrich,¹¹ is well known But in producing fistulas of the pancreas in dogs by morphine anesthesia, and injecting ether, alcohol and hydrochloric acid into the duodenum one after another, we found that ether and alcohol do not cause any secretion of the pancreatic juice, while hydrochloric acid always causes a profuse secretion Therefore, the stimulating power of ether and alcohol in human subjects is but reflex in nature and has nothing to do with the mechanism of secretion

A general survey of the results is shown in table 2

A more detailed description is necessary in order that the results may be analyzed

TABLE 3—*Enzymatic Efficiency of the Duodenal Return in a Three Hours' Collection with and Without Stimulants*

Stimulants	Amount of Duodenal Return, Cc	Trypsin, Kilo Units	Amylase, Kilo Units	Lipase, Kilo Units	Bile Pigment, Mg
None	115.7	68.5	169.3	162.6	12.4
Alcohol	109.6	71.1	97.8	125.2	15.2
Ether	134.5	61.6	134.2	116.6	18.9
Water	115.7	61.4	181.8	117.1	15.4
Hydrochloric acid	170.5	85.6	191.8	201.9	16.1
Average	123.0	70.1	145.0	151.0	14.9

Enzymatic Efficiency of Three Hours' Collection by Various Stimulants—As stimulants we used 30 cc of alcohol (10 per cent), 3 cc of ether and water and 30 cc of hydrochloric acid (0.2 per cent), and compared the results with those obtained without stimulants The average results are shown in table 3 It is seen that alcohol, ether and water have little, if any, influence on the enzymatic efficiency in a three hours' collection, alcohol tending to decrease slightly on amylase and lipase, and hydrochloric acid causing a slight increase in the three enzymes The process of secretion, however, varies with the different stimulants, it is usually more profuse in the first hour, markedly less in the second hour and increases again in the third hour This relation is shown in table 4

Age—The cases in which estimations were made occurred in patients, aged from 16 to 62 From table 5 it is obvious that on the average the enzymatic efficiency is high in patients of the ages from 20 to 40, in those less than 20 and more than 40, it is somewhat less

11 Katsch, G., and von Friedrich, L. Bauchspeichelfluss auf Aetherreiz, Klin Wchnschr 1 112, 1922

Sex—The estimation was carried out on thirty-six male and twenty-four female patients. The results show that on the average the amount of the duodenal return and the efficiency of the three enzymes are apparently less in females than in males as is shown in table 6.

Normal Enzymatic Efficiency in Three Hour Method—The results obtained with this method are given in table 7. From these results it seems justifiable to place the normal enzymatic efficiency of the duodenal

TABLE 4—Deflection of the Secretion and the Enzymatic Activity

Stimulants	Amount of Duodenal Return			Trypsin			Amylase			Lipase		
	1st Hour, Cc	2d Hour, Cc	3d Hour, Cc	1st Hour, Kilo Units	2d Hour, Kilo Units	3d Hour, Kilo Units	1st Hour, Kilo Units	2d Hour, Kilo Units	3d Hour, Kilo Units	1st Hour, Kilo Units	2d Hour, Kilo Units	3d Hour, Kilo Units
None	40.7	35.1	40.7	21.8	16.9	29.7	60.5	15.1	65.5	55.1	0	91.2
Alcohol	53.2	25.7	30.7	35.8	15.7	18.2	17.6	21.0	22.9	55.7	0	5.1
Ether	67.1	26.0	11.4	33.0	11.9	25.5	11.9	11.1	17.1	76.9	11.8	1.0
Water	55.9	31.2	60.5	19.4	11.1	36.6	65.5	18.1	70.5	12.7	11.1	5.1
Hydrochloric acid	87.8	58.9	43.8	55.5	21.6	25.5	95.0	16.0	95.8	76	11.0	17.5
Average	51.4	31.2	39.9	27.6	16.5	24.1	59.5	15.9	19.7	18.1	5.5	11.8

TABLE 5—Relation of Age to Pancreatic Secretion

Age	Cases	Amount of Duodenal Return, Cc	Trypsin, Kilo-Units	Amylase, Kilo Units	Lipase, Kilo Units	Bile Pigment Mg
16-20	12	126.6	66.1	118.5	177.2	9.6
21-30	19	123.0	70.3	156.7	148.7	11
31-40	12	125.6	79.5	150.7	156.3	18.8
41-62	7	128.7	60.2	135.0	79.8	19.2

TABLE 6—Relation of Sex to Pancreatic Secretion

Sex	Cases	Amount of Duodenal Return, Cc	Trypsin, Kilo Units	Amylase, Kilo-Units	Lipase, Kilo Units	Bile Pigment Mg
Male	36	132.2	77.1	161.2	160.0	17.2
Female	14	99.4	51.9	107.3	127.0	9.0

return in three hours at from 30 to 120 kilo-units for trypsin and from 50 to 300 kilo-units for amylase and for lipase. The average value of the normal results thus becomes 70 kilo-units for trypsin and 140 kilo-units for amylase and for lipase. Perhaps it is possible to determine the normal values in relation to age and sex more precisely. In addition, the size of the body seems also to be an important factor. In the present work, however, we are not ready to give such detailed information.

Degree of Enzymatic Activity—As already mentioned, the degree of enzymatic activity as determined in short periods gives little information as to the pancreatic activity. But if one estimates the enzymatic activity

of every half or one hour collection separately for three hours and determines the highest value, the result is fairly consistent and may be used in judging the pancreatic activity. The results thus obtained in fifty cases are given in table 8. These results show that over 500 units is the normal value for trypsin, and over 600 units for amylase and for lipase, if one selects the highest value of fractionally estimated enzymatic activity.

Amount of Duodenal Return—The amount of the duodenal return ranges from 40.5 to 277 cc, the average being 123 cc. Age apparently does not influence the amount of the duodenal return in patients from

TABLE 7—Results Obtained as to Normal Enzymatic Efficiency in Three Hour Method

Enzyme	Kilo-Units	No. of Cases	Percentage
Trypsin	Under 30	1	2
	30 to 120	48	96
	Over 120	1	2
Amylase	Under 50	1	2
	50 to 300	48	96
	Over 300	1	2
Lipase	Under 50	5	10
	50 to 300	41	82
	Over 300	4	8

TABLE 8—Results of Fractional Estimations of Enzymatic Activity in Fifty Cases

Enzyme	Units	No. of Cases	Percentage
Trypsin	Under 500	2	4
	Over 500	48	96
Amylase	Under 600	0	0
	Over 600	50	100
Lipase	Under 600	4	8
	Over 600	46	92

16 to 62 years of age. Sex, on the contrary, shows a distinct influence, the return being much less in females.

Bile Pigment—The fluctuation in the amount of bile pigment in a three hours' collection is marked, so that it is difficult to find a normal value. The range is from 2.5 to 61.7 mg, being over 5 mg in 86 per cent of the cases. The average value is 14.9 mg, and it is practically the same with each of the different stimulants used, it is somewhat less when no stimulant is applied (12.4 mg). The average in females (9 mg) is distinctly less than that in males (17.2 mg). It seems to increase with the age, as is shown in table 5.

SUMMARY

1. A quantitative method for the estimation of pancreatic function is described. Perhaps this is the first attempt to estimate the pancreatic function quantitatively in its real meaning. The enzymatic efficiency for

a fixed time is determined by multiplying the degree of enzymatic activity by the amount of duodenal return collected. After various considerations of the difficulties and failures, we chose a three hour method, which seems most reliable. The normal value thus obtained from a study of fifty patients is from 30 to 120 kilo-units for trypsin, and from 50 to 300 kilo-units for amylase and lipase. The average value of the normal results becomes 70 kilo-units for trypsin and 140 kilo-units for amylase and lipase. Alcohol, ether, water and hydrochloric acid are applied as stimulants. Alcohol and ether stimulate the outflow at the beginning, but do not have a marked influence on the whole enzymatic efficiency in a three hour study. Hydrochloric acid seems to increase the output slightly.

2 The degree of enzymatic activity of the duodenal return collected in a short period gives but little information concerning the pancreatic activity. But if the estimation is carried out fractionally every half hour or every hour separately for three hours, and the highest value is found, the result is fairly consistent being over 500 units for trypsin and over 600 units for amylase and lipase.

3 Age seems to have some influence on the enzymatic efficiency, it is highest between the ages of 20 and 40, and is somewhat less before and after those ages. The influence of sex is more obvious, the enzymatic efficiency being much less in the female sex.

4 The amount of the duodenal return does not seem to be influenced much by age in patients from 16 to 62 years old. The influence of sex is apparent, the amount being much less in females.

5 The amount of bile pigment ranges widely, so that it is difficult to find a normal value. From the average value, it is judged that the amount of the bile pigment increases with age and shows distinctly higher values in the male sex.

GASTRO-INTESTINAL REACTION TO THE EMOTIONS

THE RÔLE OF THE VEGETATIVE SYSTEM

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This paper is the third in a series of studies made on 300 women patients with psychoses¹. As the data accumulated I was confronted with the problem of a search for causes to explain the results of normal or increased gastric and intestinal function found in many of the depressed patients. The first step led to a study of the types of human emotions, the second, to a consideration of the rôle of the vegetative or involuntary nervous system, which is intimately bound up with the endocrine glands to form the vegetative system, the third, to a brief sketch of the newer ideas in regards to the mechanism of digestive function. Finally, an attempt was made to secure as simple and sound a theoretical basis for the work as possible and to formulate in the conclusions principles that would serve to explain the results obtained. These conclusions will be found to agree with the physiologic conception of those writers who stress the primary importance of the neurovegetative and endocrine systems in the determination not only of highly complex emotional states, but of disordered visceral function as well.

EMOTION

In MacCurdy's² phraseology, a complete emotion is a combination of subjective affect and objective emotional expression gestures, postures, facial movements, vocal expression and modulation, and many visceral changes. Affect is the most central and vital element in an emotion, "infinitely and eternally subjective". McDougal³ said "Affect denotes the emotional-conative aspect of all mental activity, with the recognition that feelings of pleasure or pain are conditioned by and in turn act upon the course of such mental activity, furthering or check-

* Read before the Section on General Medicine, of the College of Physicians, of Philadelphia, Nov 30, 1927

¹ From the Pennsylvania Hospital, Department for Mental and Nervous Diseases, Philadelphia

1 Farr, C B, and Lueders, C W. Gastric Secretory Functions in the Psychoses, Arch Neurol & Psychiat 10 548 (Nov) 1923. Farr, C B, Lueders, C W, and Bond, E D. Studies of Gastric Secretion and Motility in Mental Patients, Am J Psychiat 5 93 (July) 1925

2 MacCurdy, J T. Psychology of Emotions, Morbid and Normal, London, Harcourt Brace & Company, 1925

3 McDougal, W. Outline of Psychology, New York, Charles Scribner's Sons, 1923

ing it in proportion to their intensity" Affectivity, according to MacCurdy, is the determining element in our acts and omissions, directing our attention as well as our whole behavior, and determining the direction of our endeavors, while logic and judgment seem only the servants that show the way to the goal and furnish the necessary apparatus The affective faculties represent the emotional propensities peculiar to man Affectivity, when unusually responsive and in the presence of defective reflective power, causes by its exaggerated action morbid syndromes as seen in the psychoses

McDougal divides emotions into primary, secondary and derived Primary emotions owe their specific qualities largely to the visceral sense impressions made by the bodily adjustments that accompany instinctive strivings Secondary emotions are made up of blended primary emotions, which, in turn, are made up of two or more instinctive impulses excited simultaneously Derived emotions or feelings arise in the course of the operation of any strong impulse or tendency, the emotion being dependent on or derived from the working of the impulse taking the form of desire These emotions arise only in the course of actively prompted and sustained desire In short, the derived emotions are affections and feelings, in the strict sense of the word, resulting from fundamental feelings of pleasure or pain and accompanied by developed powers of imagination and an intellectual capacity to conjoin pleasure with pain

MOODS

An emotion normally subsides into a mood before the excitement wholly passes away Mood is the persistent emotion prolonged after any thought of the object Persistent moods may become morbid, as in the affective states of the neurotic and the psychotic Moods, by their repetition of corresponding conceptions, sustain the affect at the expense of effect on somatic and visceral expression until a level is reached at which there is an entire absence of reaction at the lower level⁴

Some moods are largely due to organic conditions, which in chemical and in other ways predispose the subject to this or that kind of emotional excitement In cases of long persistent morbid moods one naturally suspects the presence of an organic factor,³ as in the affectful ideas of the manic-depressive patient As Jackson describes him "The manic-depressive swings from pole to pole in his thinking as the chemistry of the body, acting through the vegetative system upon brain and other viscera, gives him the feeling of exaltation and then the awful torture of depression"

4 Lodholz, E Fear, Its Beneficial and Harmful Effects on Body Function, *Internat Clin*, 1925, vol 3, *Instincts in Domesticated Animals and Their Diseases*, *J Am Vet M A*, August, 1925, vol 67

Bleuler⁵ said

While disturbances of the affects may depend upon changes in the brain or in the chemistry of the organism, a certain constitution, usually congenital, seems to be a prerequisite in most cases. The hysteric, the paranoic are born different from healthy people. In all mental diseases the symptoms are largely an expression of the affective condition. Congenital anomalies, injuries and diseases of the brain, disturbances of nutrition, intoxications and infections plus the prolonged action of affects form, in varied array and admixture, the basis upon which psychopathic reactions occur.

VEGETATIVE SYSTEM

The pathway for emotional reaction on visceral function is the vegetative system. This comprises the neurovegetative system (also called the autonomic or involuntary nervous system) and the endocrine system. The endocrine glands appeared before the outbudding of the involuntary nervous system, regulating body metabolism by hormonal control. Later, these two great divisions joined under one system to regulate and maintain particularly all visceral function of tone, motility, glandular activity, sensitivity and absorption.

NEUROVEGETATIVE SYSTEM

The central gray matter, or midbrain, which surrounds the third ventricle, or hollow space of the primary anterior vesicle of the brain is, according to Muller,⁶ supposed to be the seat of the elementary vital and vegetative functions of life. On both sides of the third ventricle lies the optic thalamus, the old important center of the whole sensibility. In the medulla or bulb, the enlarged portion of the cord, at its junction with the midbrain or mesencephalon, is localized the important centers of respiration and circulation. It is by outgrowth from the midbrain and medulla and the neural crest of the embryonal brain stem that the vegetative nervous system developed, to form three distinct groups of neurons: one with its origin in the midbrain and bulb, one from the neural crest to form the lateral ganglia, connected with the thoracic and upper lumbar segments of the cord, and a third in the sacral segments of the cord. The middle group is called the sympathetic nerves, the remaining two, the parasympathetic. The third, seventh, ninth and tenth cranial nerves and the pelvic nerve (nervus erigens) form the latter division of the system. The vegetative nervous system remains connected by afferent and efferent fibers with the central nervous system, so that one may affect the other. Moreover, a number of specialized vegetative nerve cells remain within the cerebrospinal axis, thereby

5 Bleuler, E. Text Book of Psychiatry, New York, The Macmillan Company, 1924.

6 Von Muller, Friedrich. Anatomy of the Brain from a Clinical Point of View, Am J M Sc **175** 1 (Jan) 1928.

accounting for the occurrence of vegetative phenomena in certain diseases of the brain

PARASYMPATHETIC AND SYMPATHETIC NERVES

The vagosacral fibers, or parasympathetic nerves, when stimulated increase visceral motor and secretory activity. The sympathetic nerves inhibit visceral function, except to some structures like the pilomotor muscles, sweat glands, most of the blood vessels, fallopian tubes, uterus, vagina, vas deferens and seminal vesicles and ureters, to which no parasympathetic fibers travel, here the sympathetic nerves may either increase or inhibit motor or secretory activity. With attention directed in the present study to the gastro-intestinal tract, the vagosacral fibers running to the intestine end in ganglions in the muscle coats and mucus, the plexuses of Auerbach and Meissner, respectively. The sympathetic or splanchnic nerves originate in the thoracolumbar region of the spinal cord with their cell stations in the lateral ganglions on each side of the vertebral column, and also in the collateral ganglions grouped to form especially the celiac or solar plexus and the inferior mesenteric plexus. The sympathetic nerves are connected by white and gray rami to the spinal nerves of the voluntary nervous system, supplying the skin and muscles of the torso and extremities. The parasympathetic nerves are connected to certain of the cranial nerves, but especially to the fifth or trigeminal. The two systems are assumed to be in a state of equilibrium, similar to that in an alternating current, of stimulation and inhibition. An excitability of the vagosacral side is called vagotonia, of the sympathetic, sympathicotonia. An atony or paralysis of one side will cause a relative toniccy of the other side.

*Vagotoma*⁷—The vagotonic type of person is reserved and cold-blooded, and has a slow pulse, hypotension, contracted pupil, deep, closely set eyes, a cool pale skin which sweats easily and patchily and clammy hands and feet. He is subject to hyperchlorhydria, spastic colon, low blood sugar, hyperinsulinemia, calcium deficiency, chronic anaphylactic states, hay-fever, asthma, angioneurotic edema, urticaria, migraine and epilepsy and vertigo. He is relieved by the administration of atropine, ephedrine, calcium, ammonium chloride, parathormone and reduction of the intake of sodium.

Sympathicotoma—The sympathicotonic person is lively and excitable, with a rapid heart rate, hypertension, dilated pupils, rosy color, warm dry skin and prominent eyes, he has a high blood sugar. He tends to suffer from slow digestion and atonic constipation due to stasis, spasm of various sphincters, eczema, pruritus, hyperesthesias, myalgias and

⁷ Stewart, Sir J. P. Vegetative Nervous System, Oxford Medicine, New York, Oxford University Press, 1921, vol. 6, p. 45 (suppl. to 1927)

pains over the main arterial trunks. The appearance of many such persons suggests hyperthyroidism. There is a deficiency of magnesium. They are relieved by pilocarpine, magnesium and morphine. The sympathetic nervous system with its connections with the thyroid and suprarenal glands, liver, brain, skeletal muscles and cardiovascular system is stimulated by fear, anger, shock or pain to form the mechanism of defense, attack or flight, and of the conservation of visceral function by inhibition.

ENDOCRINE SYSTEM

The inter-relationship between the various endocrine glands and the effects of their hypersecretion or hyposecretion on the body generally are being worked out in many laboratories. Established facts are still comparatively few, except for the action of a single gland on bodily functions of growth, nutrition, resistance to disease, metabolism, procreation and vascular tonus. These effects may be brought about by action on the vegetative nervous system, direct or indirect chemical action, or by a combination of nervous and chemical stimuli. However, the endocrine glands play an all important rôle.⁸ This is seen not only in the evolution and growth of the organism as a whole, but in the regulation of the functioning of its various component parts, which, when exercised in a normal manner, conserves the constitution of the body, nourishes the activity of vital processes and, by providing a self-regulating mechanism for the body, sets the voluntary nervous system free for the execution of its essential function, namely, volitional response to changes in the environment.

Any disturbance in the balance of the neurovegetative system, unless compensated, causes a disturbed equilibrium in the endocrine system, and any uncompensated endocrine imbalance is reflected in the vegetative nerves. Equilibrium in vegetative structures, however, depends very much on the colloidal complex of the cell and its contents in ions, for nerve impulses and chemical substances circulating in the blood and tissue juices produce different effects, depending on the difference of the chemical and physical condition of the cell.⁹

DIGESTIVE FUNCTION

Secretion—According to Ivy,¹⁰ gastric secretion can be divided into three phases with reference to cause: (1) the cephalic phase, caused by (a) reflexes through the cerebrum (psychic) and by (b) reflexes

8 Stewart, T. G. *Vegetative Nervous System*, Oxford Medicine, 1921, vol. 6, p. 829 (suppl. to 1927).

9 Pottenger, F. M. *Symptoms of Visceral Disease*, St. Louis, C. V. Mosby Company, 1925.

10 Ivy, A. C. *Contribution to the Physiology of the Stomach*, J. A. M. A. 85: 877 (Sept. 19) 1925.

through the thalamus, midbrain and medulla, excited by sight, taste and smell of food in the presence of appetite, (2) the gastric phase caused by (a) mechanical distention of the stomach and (b) the action on or by way of the gastric mucosa of substances in the food, (3) the intestinal phase, caused by the action on or by way of the intestinal mucosa of substances in the food or resulting *de novo* from digestion. Meat is the only food thus far studied that contains a substance that stimulates on contact with the gastric mucosa. A humoral mechanism is concerned with gastric digestion.

Psychic Secretion The vagi are the efferent nerves concerned in conducting the impulses from the gastric secretory center or centers to the gastric glands. The afferent nerves carry sensations of sight, taste and smell to the centers, the act of chewing and swallowing probably plays the rôle of decreasing the threshold of the reflex arc concerned. Busik¹¹ found that irritation of the secretory center from increased intracranial pressure due to tumor of the brain caused increase in gastric acidity, and that involvement of the same center in the degenerative process of epidemic encephalitis caused a reduction in gastric acidity. Gastric motility was unaffected in both types of patients. Pavlov¹² expressed the belief that the vagal stimulation is the predominant contribution to acid secretion through both digestive and interdigestive phases. In vagotonia, there is a continuous hypersecretion of highly acid juice through the fasting and digestive phases.

Hunger and Thirst—These are feelings that result from visceral sensations and instinctive motives arising to consciousness in the cerebral centers of hunger and thirst, and which are aroused by association centers of sight, taste and smell. When intensified by a craving to gratification, the same sensations and instinctive motives stimulate secretory and motor centers, which send specific nervous impulses through the vagi to the musculature and glandular structures of the intestine (Hollander)¹³

As local conditions of the stomach may destroy or increase the feeling of hunger or thirst, so central irritation or disease may give rise to a ravenous appetite or thirst or to a complete loss of the same. Gluttony may be associated with disorder and disease of the gastro-intestinal tract, and anorexia with increased visceral function. Thirst is characteristic of disorders of the pancreas and pituitary gland.

Injection of food into the colon, the nutritive enema, appears to satisfy hunger or thirst through nervous pathways before sufficient absorp-

11 Busik. Secretory Function and Motility of the Stomach in Brain Diseases, *Russk Klin* 6 353 (Sept) 1926

12 Pavlov, J. P. Work of the Digestive Glands, London, 1902

13 Hollander, B. In Search of the Soul and Mechanism of Thought, Emotion and Conduct, London, 1920

tion can possibly take place. Carlson¹⁴ found hunger contractions of the stomach dependent on a deficiency of dextrose in the blood serum, and Muller,¹⁵ that hunger and thirst may be produced when the amount of protein in the blood serum sinks as low as found in patients with severe inanition. Hunger and thirst can be excited by posthypnotic suggestion. Healthy subjects who have just eaten a hearty meal can be made to feel fresh hunger and go through another meal. Further, it is possible to satisfy the hunger and thirst of subjects in deep hypnosis by merely suggested food and drink.

Anorexia—Refusal to eat is the most important etiologic factor following emotional upsets, with digestive symptoms following. This is called primary mental anorexia, and consists in the progressive loss of the mental representation of appetite (Dejerine).

Loss of appetite has been induced by suggestion to such an extent and for so long a period that the person concerned refused solid food for fourteen days. By autosuggestion the psychotic patient sometimes refuses to take nourishment from a great variety of motives, according to the form of the psychosis. A patient may be immersed in his thoughts so that the sensation of hunger is deadened, he may refuse it because he fears it is poisoned, because a voice told him he must not touch it or because he is too great a sinner. In each instance there is the same symptom of suppression or perversion of the sensation, associated with different motives.

Motility—The gastro-intestinal tract is essentially an automatic organ like the heart. Auerbach's plexus, ganglions lying between the longitudinal and circular muscle coats, is the intrinsic nervous mechanism that originates the power of tonus, rhythmicity and irritability. However, motility of this type would be functionally inadequate in the absence of control of the central nervous system by way of the vagosympathetic system. The latter converts an inherent mechanical regularity into a modulated and extremely variable activity of rhythm, tone and amplitude of contractions, adapting gastro-intestinal functional responses to the constantly changing nervous and chemical activities in the body as a whole (Thomas).¹⁶ The intrinsic or enteric neuromuscular system is affected by acute and chronic debilitating, depressed nutritional and asthenic states, by chemical disorders, by disorders of the endocrine system and by drug reactions.

Tonus—Gastro-intestinal tone is dependent on both nervous and chemical factors.⁹ As long as the muscle is in continuity with the nerve

14 Carlson and Litt. Visceral Nervous System, Reflex Control of Pylorus, Arch Int Med **33** 281 (March) 1924.

15 Muller, L. R. Das vegetative Nervensystem, Berlin, 1920.

16 Thomas, J. E., and Kuntz, A. A Study of Gastro-Intestinal Motility in Relation to the Enteric Nervous System, Am J Physiol **76** 606 (May) 1926.

cell which nourishes its nerve, the action of that nerve cell keeps the muscle in a condition of tone. Certain chemical substances, especially the salts of sodium, maintain the continuity of the muscle with the nerve cell. Sympathetic (inhibitory) activity is enhanced by the presence of calcium and parathyroid, parasympathetic or vagosacral activity by potassium, sodium and magnesium. Normal activity of rhythm and tone requires definite relative amounts of these important ions.

Vascular Tonus—The splanchnic vessels supply the abdominal and pelvic viscera. They are of greatest importance in the maintenance of blood pressure and in the circulation of the blood. The splanchnic vessels are the storehouse for surplus blood when not required by body activity. When special activity on the part of any organ is required, the splanchnic (sympathetic) nerves by local overstimulation produce a vasodilatation by paralysis of the blood vessels of that organ, during the stage of its activity, thus increasing motor and secretory function. The splanchnic nerves may likewise, by sympathetic inhibition, cause an increase in vasomotor tone of the splanchnic vessels to produce a decrease in motility and secretion, locally or through the entire alimentary tract.¹⁷ A spastic condition of the capillary bed in the gastric mucosa causes a temporary achylia, a paralytic vasodilatation causes a hypersecretion of acid and mucus. Krogh has shown that the vascular bed in a muscle in activity contains thirty times the quantity of blood found in the same muscle when inactive.

Epinephrine,⁹ when poured into the blood in small quantities, causes by its peripheral effects constriction of the vessels of the skin, the mucous membranes and the abdominal organs, driving the blood into the vessels supplying the skeletal muscles, the vessels become actively dilated for its reception through the effect on the mechanisms of the sympathetic and dorsal root ganglions. But as the quantity of liberated epinephrine accumulates, the peripheral effect begins to overcome the ganglionic effect in the skeletal muscles, the intestinal or splanchnic vessels by increased action of the collateral sympathetic ganglions (solar plexus), and the inferior mesenteric plexus begins to dilate and the blood is reversed in its path.

The Problem—Having accumulated these hypotheses, theories and facts, a search was undertaken to discover from among them cause or causes to explain the practically normal average, and even increased, secretory and motor function in 300 patients with psychoses. It was of course recognized that the diagnosis of the psychosis did not lend itself as an approach to the solution from the standpoint adopted for the present study, namely the interpretation of the gastro-intestinal func-

¹⁷ Kerppela, W. Vaso-Motor and Nervous Factors in Nervous Disease, Arch f Verd Krank **38** 143 (June) 1926

tional observations as emotional reactions. So the patients were grouped according to the affective states exhibited by them at the time the gastro-intestinal studies were being performed. The patients, according to their affectivity, fell most readily into one of seven groups: depressed or previously depressed, the apprehensive, the confused, those without affect, the exhilarated and the unclassified.

It may be of interest to restate conclusions expressed in the second study after a gastro-intestinal survey of 191 psychotic patients. They were as follows:

1 Secretory function did not bear any relation to nutrition in this series. Obesity, however, was more often associated with hyperchlorhydria.

2 Long continued depression, as such, has no well defined effect on secretion.

3 Patients in whom restraint and nasal intubation were necessary showed the highest degree of secretion and acidity.

4 Physical and nutritional factors, rather than psychic, were responsible for disorders of gastro-intestinal motility.

5 Position and tonus seem to have less bearing on gastric motility than would be anticipated.

6 Malnutrition per se is not suggestive of any particular affective state.

7 Of those patients with hypersecretion or hyposecretion, 7 per cent had, possibly, etiologic somatic diseases. Of those patients with normal secretion, 3 per cent were suffering from somatic diseases.

TABLE 1—*Percentage Acidities in the Affective Groups**

Group	Number	High	Normal	Low	Achylia
Depressed	122	28	48	11	13
Not depressed	178	25	51	17	7
Total	300	26	50	15	9

* There is practically no percentage difference between the two groups: high acidity, 65 per cent or over; achylia, no free hydrochloric acid or pepsin in fasting and 12 fractionals. High figures were taken at hour fractional (45 minute to 75 minute period).

TABLE 2—*Percentage Acidities in the Nondepressed Groups*

Group	Number	High	Normal	Low	Achylia
Apprehensive	56	23	50	22	5
Previously depressed	26	23	46	20	11
Confused	12	17	50	17	16
Unclassified	19	17	68	10	5
Psychomotor activity	21	29	52	17	2
No affect	44	32	48	16	4
Total	178	25	51	17	7

TABLE 3—*Percentage Acidities in the Depressed Groups*

Group	Number	High	Normal	Low	Abnormal
Retarded	37	27	51	3	19
Agitated	57	28	46	15	11
Catatonic	5	20	60	0	20
Confused, apprehensive	23	30	44	13	13
Total	122	28	48	11	13

TABLE 4—*Percentage Motility in the Affective Groups**

Group	Number	Rapid	Normal	Delayed
Depressed	46	9	52	39
Not depressed	79	6	58	36
Apprehensive	32	6	60	28
Remainder	47	6	53	41

* Results are taken from roentgen-ray studies on 125 patients for intestinal motility. Again there is practically no percentage difference between the two main groups. Greatest delay was found in patients not depressed or apprehensive (11 per cent).

TABLE 5—*McDougal's Classification of Instincts and Emotions (Abridged)**

Instincts	Primary Emotions	Derived Emotions
Flight	Fear	Confidence, hope
Fight	Anger	Anxiety
Parental	Tender emotion	Despondency
Reproductive	Sexual	Despair
Food seeking	Hunger, appetite	Regret, remorse
Repulsion	Disgust	Sorrow, grief
Appeal	Distress	Joy
Curiosity	Wonder	Elation
Submission	Inferiority	Pity
Assertion	Superiority	Surprise
Social	Loneliness	

* In this classification the list of primary emotions are related to the list of instincts, the derived emotions listed are unrelated to the instincts or primary emotions.

TABLE 6—*Sympathicotonia—from Fear—Adrenal Overactivity**

Dilatation of pupils	Erection of hairs
Parched lips and tongue	Loss of voice
Constriction of blood vessels	Loss of muscle tone
Inhibition of alimentary function	Paralysis of sphincters
Tachycardia, hypertension	Twitching lips
Air hunger (suprarenal stimulation of respiratory center)	Pallor, pruritus
Liberation of sugar from liver	Tremors, skeletal muscles
	Hypo insulinemia

* Sympathicotonia, whether from fear, pain or toxemia causes an increase in visceral reflexes by way of the dorsal root ganglions to the thoracolumbar somatic distribution to the skin, recti and spine.

TABLE 7—*Symptoms of Vagotonia**

Contracted pupils	Sodium, magnesium, potassium excess
Bradycardia, hypotension	Increase in saliva
Reflex vomiting	Hyperhidrosis, bromidrosis
Hypersecretion, hyperacidity	Insomnia, tinnitus
Spastic colon, mucous colitis	Hypertonicity, hyperperistalsis
Anaphylactic states	Asthma, urticaria, food allergy
Calcium, parathyroid deficiency	Migraine, epilepsy, hyperinsulinemia

* Increase of visceral reflexes to all structures supplied by the vagosacral system: eyes, pharynx, heart, gallbladder, lungs, appendix, muscular coats of the intestine and pancreas, distribution of fifth nerve.

TABLE 8—*Gastro-Intestinal Symptoms of Vagotomy and Sympathectomy*^a

Salivary glands	Decrease in watery content	Stimulates watery content
Stomach	Decrease in motility and secretion, including hydrochloric acid, controls blood vessels	Increase in motility and secretion, including hydrochloric acid
Intestinal tract	Relax musculature and decrease secretion, controls blood vessels	Stimulate musculature and increase secretion
Sphincters pylorus,* ileocecal, anal	Contract exactly opposite action on rest of musculature, gastro-intestinal tract	Relax exactly opposite action on rest of musculature, gastro-intestinal tract

^a According to Carlson and Litt (*Arch. Int. Med.* 33: 281 [March] 1924), motor and inhibitory nerve fibers enter the pylorus by way both of the vagi and of the splanchnic nerves (confirming previous observers)

TABLE 9—*Sympathectomy—Due to Toxemia*^{*}

Malaise	Constipation	Lack of endurance
Aching	Loss of weight	Loss of strength
Chilliness, rigor	Rapid pulse	Muscle twitchings
Anorexia	Increased blood pressure	Nerve instability
Digestive disturbances	Sweats	Vasoconstriction
(a) Hypomotility	Rise in temperature	pallor
(b) Hyposecretion	Leukocytosis (polys)	
Severe toxemia vasodilatation, marked sweating, subnormal temperature, collapse as in nicotine poison, intestinal obstruction		

^{*} Pottenger *Symptoms of Visceral Disease*, p. 73

COMMENT

The gastro-intestinal reaction to an emotion, or better the gastro-intestinal contribution to a complete emotion, depends on the condition of the neurovegetative system, the endocrine system and the chemical and ionic changes in the cells and fluids bathing the cells of the alimentary tract. It has been generally accepted by psychologists and physiologists that these mechanisms, stimulated to action by acute primary and secondary emotions, such as fear, anger, pain, horror and repulsion, as well as the acute derived emotions of anxiety, despondency and despair cause an inhibition of secretion and motility, while the object arousing the emotion is still in consciousness. The sympathetic division of the neurovegetative system intimately correlated with certain of the endocrine glands, especially the suprarenals, is the specific mechanism of inhibition of digestive function. These emotions, by liberating an excess of epinephrine into the blood stream or by acting on the sympathetic ganglions, liberate sugar from the liver cells into the blood to such an extent as to cause transient glycosuria. Energy is thus supplied to the muscles for the physical struggle that may be called forth by the emotion, especially of fear or rage which results in flight or fight. On account of social restraints, this sympathetic or defense mechanism has outlived much of its usefulness. The aroused mechanism unsatisfied by instinctive action is forced to convert itself into irascible or fearsome dispositions. In disease, however, it is called on in the struggle against toxemia

and inflammation and infection Cannon¹⁸ separated the sympathetic ganglions from the communications with the spinal cord in a cat, the animal continued in apparently normal health

The high percentage of normal figures for secretion and motility, even in groups of depressed persons, was maintained as the number of psychotic patients studied was increased One then realized that the pathologic affective states found in many psychoses could not be interpreted as the subjective expression of simple acute emotions A necessary corollary was that one could not satisfactorily explain the gastro-intestinal reactions in all those patients as simple emotional concomitants

Granting that the emotions were real, even to the production of external expression, such as weeping, moaning, screaming or laughing, I was led, nevertheless, to the conjecture that the objects exciting them were no longer in consciousness, just as in the moods Without an exciting object, emotional expression in the viscera could scarcely be expected Again, the conception arose that when the affective portion of a complete emotion is overexpressed or overestimated subjectively, visceral expression is correspondingly inactive or may fail to register

As normal visceral response to emotional stimuli is dependent, as has been shown, on the integrity of vegetative and chemical mechanisms, the association of abnormal subjective emotional reactions with normal objective visceral expression in many of the psychotic patients suggested the possibility of a derangement of this involuntary system Therefore results were aimed with a classification of the depressed groups in terms of the state of the vegetative system A search for symptoms of vagotonia was made in patients with hypersecretion, hypermotility or spasticity, for symptoms of sympathicotonia in patients with hyposecretion, hypomotility and stasis and also for endocrine dysfunction acting on the sympathetic or the vagosacral nerves

The study, preliminary to further researches on the relation of the psychoses to the vegetative nervous system, warrants the opinion that an excitability of the vegetative system was present in some patients in sufficient degree to cause not only a stimulation of the digestive function (rarely a depression of function), but to be the origin of the affective disorder as well It is generally accepted that somatic and visceral disorders and diseases may initiate subjective emotional reactions, it is just as reasonable to assume that the vegetative system may likewise precipitate or maintain abnormal affectivity In fact, one is led to believe that chronic emotionalism and morbid moods through their protraction and summation have less and less effect on visceral function,

18 Cannon, W B, Lewis, J T, and Britton, S W Dispensability of Sympathetic Division of the Autonomic Nervous System, Boston M & S J 197 514 (Sept 29) 1927

but work their greatest havoc at the higher levels. There it is that reason, intelligence, will, faith, conscience, self-control and social ideals are dominated, overwhelmed and apparently often destroyed by uncontrolled emotionalism, absolute egotism, fantasy, obsessions, hallucinations, stupor, moral inertia, stark depression and homicidal mania—the lowest reversion to sheer animalism.

Claude's¹⁰ researches on the vegetative system in 600 patients with psychoses brought him to the following conclusion:

The intensity and rapidity of morbid periods in the psychoses seem to be proportionate to the excitability of the vegetative system, probably through the intermediation of the humoral or endocrine mechanism. It is not astonishing, therefore, if a characteristic state of the neurovegetative system is to be found constantly in the organic symptomatology of certain psychoses.

Torsten Sonden,²⁰ in his monograph on somatic conditions in manic-depressive psychoses, concluded as follows:

Of the hypotheses mentioned here those seem best accounted for which connect the manic-depressive psychosis with changes in the endocrine organs or in the nervous system. The importance of the endocrine factor may either be conceived in this way, that the very cause of the psychosis is a disturbance in one or more of the endocrine organs, or else that the disturbance is localized to the nervous system, but that a certain endocrine composition is a condition for this disturbance to lead to a psychosis. Whatever may be the case the nervous system probably plays a fairly independent part in relation to the endocrine system in the psychoses. The true basis of the psychoses must probably be assumed to be a heredity disposition.

Henry²¹ said:

The results of this study might be considered evidence of definite changes in the functions of the vegetative nervous system accompanying psychoses. Psychoses represent changes in the entire individual rather than abnormal functioning of the brain or central nervous system as was formerly believed.

Crile²² stated:

There has been evolved through the ages a nerve mechanism of such infinite delicacy and precision that it can register permanently within itself every impression received in the phylogenetic and ontogenetic experience of the individual.

19 Claude, Henri, Santenaise, D., and Fargowla, Rene. An Attempt at a Biologic Diagnosis of States of Excitement and Depression, *J Neurol & Psychiat* **13** 729 (June) 1925.

20 Sonden, Torsten. A Study of Somatic Conditions in Manic-Depressive Psychosis, Uppsala, 1927.

21 Henry, G. W. Some Roentgenologic Observations of Gastro-Intestinal Conditions Associated with Mental Disorders, *Am J Psychiat* **3** 681 (April) 1924, Gastro-Intestinal Motor Functions in Schizophrenia, Roentgenologic Observations, *ibid* **7** 135 (July) 1927.

22 Crile, G. W. Origin and Nature of the Emotions, Philadelphia, W. B. Saunders Company, 1915.

that each of these nerve mechanisms or brain patterns has its own connection with the external world that emotions and thoughts and personality and memory are to be interpreted in terms of these brain patterns forming emotional patterns, etc

Finally, how reasonable it is to agree with Muller that the vital energy of the whole man is localized in the vegetative system! 'Our organs, our glands, our whole body influences our mind. The psychical processes are not localized in the brain cortex. Life and soul are a function of the whole organism, there are no sharp limits between neurology and internal medicine'

If the present study has shed but little new light on the gastro-intestinal reaction to the emotions, it has directed attention toward the vegetative system and its importance not only as pathway for emotional reaction on visceral function, and vice versa, but as a mechanism of vital and creative energy that colors and determines so great a portion of man's mental and emotional life. It is still a comparatively neglected field, because a most difficult one for the neurologist and the physiologist, it deserves the same painstaking researches as were made on the central nervous system

CONCLUSIONS

1 The gastro-intestinal reaction to an emotion persists only as long as the original object causing the emotion is present, in other words, the visceral expression of an emotion ceases when the emotion is changed to an abnormal syndrome or mood

2 Chronic affective states as seen in the psychoses are frequently not specific emotions, however intense their outward somatic expression, but are objectless and purposeless habitual or cyclic feelings, morbid moods, and the milder affective summations, the feeling tones

3 An intact vegetative system tends to maintain normal gastro-intestinal function in spite of a dominant emotionalism that has become habitual after the object of the emotional reaction has disappeared

4 A deranged vegetative system may originate a psychosis with its specific affective state—anxiety states in vagotonia, the emotional lability in sympathicotonia, the baseless fears of the involuntional melancholic, instinctive perversions in mental degenerates with the inherited stigma of overexcitability of the vegetative system, and deficient affectivity as seen in acute or chronic asthenic states, associated with atony of the neurovegetative system

5 Morbid nervous and mental states may be as markedly developed in the presence of an apparently normal vegetative system

6 Patients inherit the vegetative as well as the physical characteristics of their families, the former frequently determines the patient's emotional life

7 The gastro-intestinal function is usually not depressed in the psychoses, except when associated with somatic disorders, or when the patient is of the sympathicotonic type or has some atonic condition of the neurovegetative system

8 The gastro-intestinal function is increased in the vagotonic type of patient with a psychosis, in patients with some types of depression and in those who resist the fractional study. The increase in the last group is possibly due to a vagal stimulation of anger in a vagotonic patient, to sympathetic overstimulation by fear, causing splanchnic congestion, or to a stimulation of the secretory centers by increased cerebral pressure due to vascular engorgement

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ARTERIAL HYPERTENSION AND PHYSICAL WORK *

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The origin of high blood pressure is still not clear. Measuring the blood pressure does not give sufficient information concerning the disturbance in its regulating mechanism, which apparently results in some instances from functional changes. Repeated measurements during the day and early in the morning are of greater value, but do not yield further insight into the mechanism of hypertonic disturbances.

In recent studies¹ of presenile disturbances of blood pressure I described some new tests which, in my opinion, aid in determining the disturbances in the regulating mechanism in high blood pressure. By means of these tests, one can demonstrate the compensating power of the organs which regulate blood pressure level. The curves obtained in my labor test illustrate the regulating action of these organs, vasomotor center, vasomotor nerves, etc., which are independent of the otherwise variable blood pressure level.

The labor test is performed as follows. The blood pressure is measured at absolute physical rest, then the patient is made to ascend at a slow pace two flights of stairs. The blood pressure is measured immediately and each half minute for from ten to fifteen minutes afterward. The data obtained are registered in curves. Normal curves of young persons show a slight elevation of the blood pressure after the work is finished, amounting usually to from 16 to 28 mm, as determined by the Riva-Rocci sphygmomanometer. The increase of the blood pressure is of short duration, lasting only two or three minutes and then giving place to a slight fall to below normal compensating decrease (chart 1).

THE LABOR TEST IN HYPERTONIC STATES

In the report mentioned, it was shown that the curves of elderly men are markedly different from those of younger persons. The elevation of the blood pressure after working is greater and it lasts much longer. In this respect, the behavior of elderly person is similar to that of patients suffering from essential hypertension.

Most of the examples of hypertension observed by me were in patients with nephritis. The so-called "essential forms" of hypertension

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¹ Baráth, E. Blutdruckstudien an alternden Menschen. *Ztschr. f. d. ges. exper. Med.* 54:58, 1927.

were seldom observed. These cases were considered with a certain reserve, because roentgen-ray examination nearly always revealed marked aortic enlargement. More or less permanent hypertension was often observed in women at the climacteric. All these patients were carefully examined with special regard to the eventual alteration of the function of the kidneys. Examinations of blood pressure, including the labor and psychic tests, were made. At this time I shall comment only on

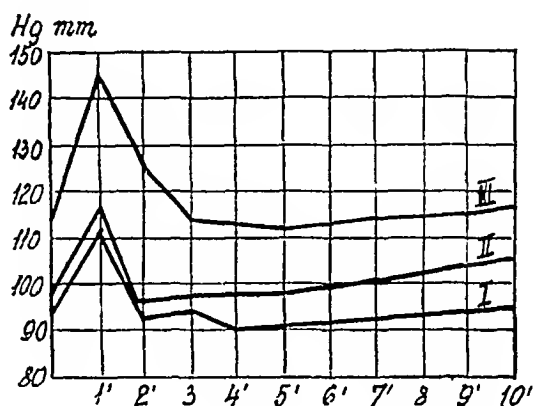


Chart 1—Increase and compensating decrease in blood pressure in young persons after work

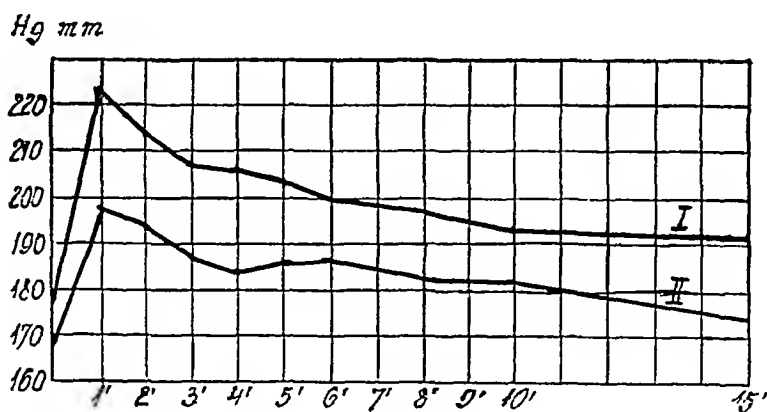


Chart 2—Blood pressure curves of persons suffering from permanent arterial hypertension

the question of the regulation mechanism of blood pressure in hypertonic patients after work

In charts 2 and 3 are seen the blood pressure curves of persons suffering from permanent arterial hypertension in nephritis. Comparison of these curves with the normal curves in chart 1 shows essential differences. The elevation of the blood pressure after work is remarkably high, an increase of from 50 to 80 mm was often found. The blood pressure level often reaches 200 mm or more, as measured by the Riva-Rocci sphygmomanometer, in patients whose normal pressure is

considerably less. Moreover, a striking alteration occurs in the form of the curves.

It has been seen in the normal curves that the elevation of the blood pressure is of short duration, in from two to three minutes, the curves reach the normal level, they usually have the form of an equilateral triangle. The curves of hypertonic patients, on the contrary, are more flat, they fall slowly and incompletely to their former level, the compensating decrease in the blood pressure is absent. A persistence of the

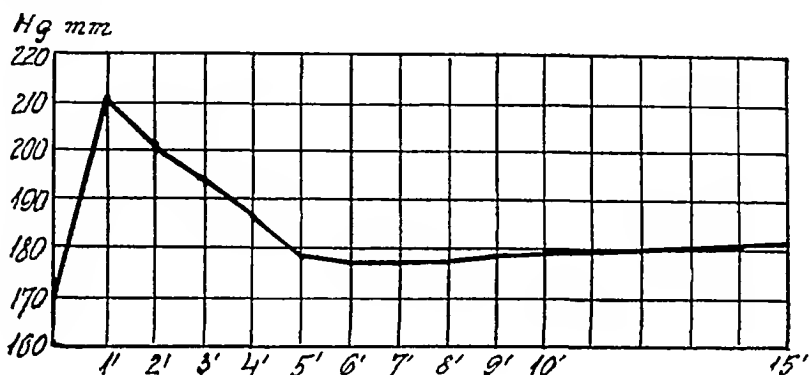


Chart 3—Blood pressure curve of persons suffering from permanent arterial hypertension

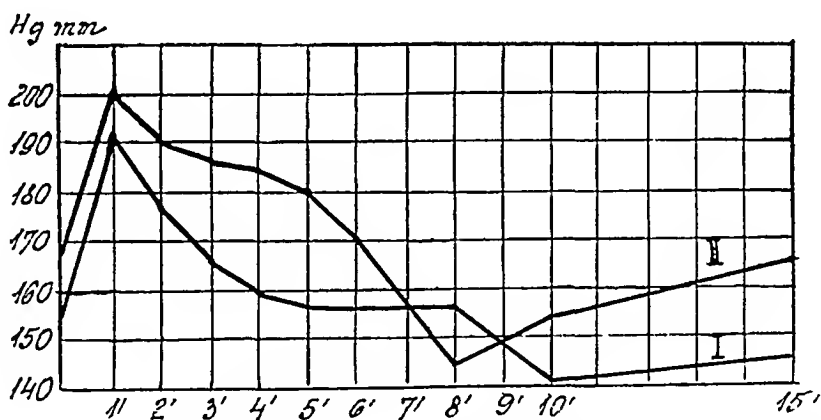


Chart 4—Blood pressure curves of persons suffering from essential or climateric hypertension

elevation of the blood pressure is often found even after from ten to fifteen minutes. This shows clearly the torpidity of the compensating function as characteristic of permanent high blood pressure.

Chart 4 shows the curves of persons suffering from essential or climacteric hypertension. These are labile forms of high blood pressure with remarkable morning depressions. The fall in the elevation of the blood pressure after work is slow in these cases also. After from five to six minutes, the blood pressure is still above the former level. Afterward, however, there is a deep depression in the blood pressure curve,

not only to its former level, but far below it. In these cases, therefore, one finds a slow, but vigorous, compensation, a tendency contrary to the torpidity of the compensating mechanism in hypertonic patients.

TWO TYPES OF ARTERIAL HYPERTENSION, AS DISTINGUISHED BY LABOR TESTS

On the basis of my experiences, I have divided the cases of arterial hypertension into two groups.

1 Permanent high blood pressure, with a slight compensating tendency of the regulating mechanism. In this group are included the cases of chronic diseases of the kidneys with hypertension (nephrosclerosis and chronic nephritis) and several cases of arteriosclerosis.

2 Labile high blood pressure with a slow, but persistent regulating mechanism. In this group are included the forms of so-called essential high blood pressure, climacteric hypertension and some forms of arteriosclerosis. The blood pressure in presenile age is labile, and the compensating power of the regulating apparatus is deficient, this justifies the attempt to include the disturbances of the blood pressure of elderly persons in the second group. Owing to the fact that an aortic enlargement is found before a considerable elevation of the blood pressure is present, alterations of the vessels and of the regulating mechanism of the blood pressure must be considered as primary.

The labor test is a great advance in the analysis of disturbances of blood pressure. On the basis of the labor test, various types of hypertonic states may be established. The disturbing fluctuation of the blood pressure level may be excluded by means of this test. It may possibly be used for the analysis of therapeutic effects. I shall report further observations in a future communication.

SUMMARY

By means of the labor test described in this paper, the study of disturbances of the blood pressure is facilitated. On the basis of blood pressure curves obtained after work has been performed (going up two flights of stairs), two main groups of cases of hypertension may be distinguished: one in which a slow and incomplete compensation of the hypertension occurs after work has been done (cases of nephrosclerosis and chronic nephritis, and some cases of arteriosclerosis) and another in which there is slow but complete compensation (essential hypertension, climacteric high blood pressure). In cases of disturbances in the regulating mechanism without permanent hypertension (presenile age), a marked enlargement of the aorta may be found, and the possibility of primary processes of the vessels and of primary disturbances in the regulating mechanism of the blood pressure is to be considered.

THE BACTERIOLOGY OF RHEUMATIC FEVER AND THE ALLERGIC HYPOTHESIS *

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AND

H YU, M D

BOSTON

Evidence of the association of the nonhemolytic streptococci with rheumatic fever has recently been much strengthened by the work of Small¹ and of Birkhaug.² Their studies have given added importance to the earlier work of Rosenow,³ Rothschild and Thalheimer,⁴ of Davis⁵ and of many others who have isolated organisms of this group from cases. Small and Birkhaug obtained organisms to which they attribute specific etiologic significance, and, in keeping with many others who have announced similar results, believe that the lesions of the disease remote from the localization of the bacteria are caused by the absorption of toxins. As opposed to this school of reasoning there has gradually developed another view, namely, that many of the manifestations of rheumatic fever are due to an allergic reaction of sensitized tissues to the antigenic materials discharged from chronic streptococcus foci, a theory which is more reconcilable with the experience that the organisms isolated at various times from rheumatic patients belong to closely related but by no means identical varieties. We have recently expressed our own views concerning this probability, and Swift⁶ has also declared himself definitely in favor of the allergic conception. Our own ideas in regard to this date back to the work of Herry⁷ and that of Faber,⁸ whom we regard as the originators of the thought that hypersensitiveness may be involved in the pathologic processes of the disease. It was particularly Faber's paper which stimulated our interest in the matter, but Faber—writing at a time when the phenomena of bacterial allergy were little understood—confused toxic allergic damage with the idea of local hyper-

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1 Small Am J M Sc **163** 101, 1927

2 Birkhaug J Infect Dis **40** 549, 1927

3 Rosenow, E C The Etiology of Auricular and Muscular Rheumatism **60** 1223 (April 19) 1913

4 Rothschild and Thalheimer J Exper Med **19** 429 and 444, 1914

5 Davis, D J Relation of Varieties of Streptococci, **58** 1283 (April 27) 1912, Davis, D J, and Rosenow, E C An Epidemic of Sore Throat Due to a Peculiar Streptococcus, *ibid* **58** 773 (March 16) 1912

6 Swift, H F, Derick, C L, and Hitchcock, C H Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, J A M A **90** 906 (March 24) 1928

7 Herry Bull Acad roy de med de Belg **28** 76, 1914 footnote 8

8 Faber J Exper Med **22** 615, 1915

sensitiveness to bacterial invasion Swift and his associates could not confirm his results in this regard and the matter was dropped for some time

It is not our intention to go into details regarding the mechanism of bacterial allergy further than to say that evidence seems to us to point toward the conclusion that the allergic state is a part of the immunologic mechanism, and, in its first stages, before antibodies have been accumulated to any extent in the circulation, the phenomenon is mainly cellular, expressing itself in an extraordinary irritability of the cells to contact with the antigen That with some bacteria, such as the streptococci, this may later develop into a true immunity or anergy—in other words, a state in which contact with antigen does not produce reactions—was indicated in our work with Grinnell⁹ on streptococcus allergy in 1925, and has since then been more definitely demonstrated by Dochez and his co-workers¹⁰ Similar work with nonhemolytic streptococci has since then been done by Andrews, Derick and Swift¹¹

In our study with streptococcus allergy in 1925, we injected guinea-pigs with living streptococci and also subjected them to implantation with living streptococci in agar—a method which, with Raymond,¹² we described for similar purposes many years ago In the studies on the hemolytic streptococci, we expressed the following view, from which we have seen no reason to depart since then

We have subjected the hemolytic streptococcus infections to a more extensive study, since these organisms by their frequent invasions of the human throat would seem to represent the most important group of bacteria with which lesions or symptoms secondary to the establishment of an allergic condition might be associated Moreover, streptococcus infections of the throat, teeth, etc, have again and again clinically forced themselves into association with various pathological lesions remote from the site of the bacterial focus In many of these conditions failure to find the organisms themselves in such injuries supposed to be secondary to the streptococcus process has suggested either a toxic or an allergic pathogenesis Such reasoning is especially applicable to the various forms of arthritis, in which it is at least logical to think of a possible allergic association or, in the light of the recent work on streptococcus toxins, of a remote toxic effect.

Following our experiments on allergy and the hemolytic streptococci, one of us (H Z) with Grinnell¹³ carried out a number of experiments in which guinea-pigs sensitized to hemolytic streptococci, and more espe-

9 Zinsser and Grinnell *J Immunol* **10** 725, 1925

10 Dochez and Sherman *Proc Soc Exper Biol & Med* **22**:282, 1924-1925, Dochez and Stevens *J Exper Med* **46** 487, 1927

11 Andrews, Derick and Swift *J Exper Med* **44** 35, 1926, Derick and Swift *Proc Soc Exper Biol & Med* **25** 222, 1927

12 Zinsser and Raymond *Proc Soc Exper Biol & Med* **18** 121, 1920-1921.

13 Zinsser and Grinnell *J Bact* **14**:301, 1927

cially to pneumococcus autolysates, were tested for sensitiveness by inoculations both into the skin and into one knee joint, under proper control. Inflammatory reactions of the joints were obtained which were in general proportionate to the degree of sensitization as indicated by the skin tests.

Pathologic examination of such joints showed heavy exudates into the joint capsules, into adjacent tissues and into the cavity of the joint. There was no necrosis, and all tissues were intact or separated by elements of exudate. The synovial epithelium could be traced as a continuous layer invaded by leukocytes in the act of migration, and penetrated by strands of fibrin¹⁴. This work on the joints was not further pursued, because we failed utterly in simulating the human condition in the sense of obtaining joint conditions in hypersensitive animals by intravenous injections or administrations elsewhere than directly into the joint.

The fact that nonhemolytic streptococci should be particularly common organisms in rheumatic fever, although we think that other organisms may also be responsible, could be explained by the consideration—more than mere assumption and based on actual observation—that the biologic balance of invasiveness and resistance established between human beings and these organisms is of such a nature as to be likely, more than most other organisms, to lead to the establishment of chronic foci.

Two of the premises in the allergic reasoning are—one, the establishment of foci in regions not accessible to cultural examination during life, which would explain the many negative bacteriologic investigations in rheumatic cases and the irregularity of observations on blood culture, and the other, the multiplicity of the strains of these streptococci, which can be found in connection with rheumatic cases, and which has been thoroughly studied by Swift and his co-workers.

Since a study of cases in human beings is the most direct support of any theory that has bearing on a disease of man, we wish in this paper to add to our former experimental consideration of this subject a report of a number of cases which illustrate these points and which seem to us to have particular significance in their contrast to the work of Small and Birkhaug.

REPORT OF CASES

CASE 1—J. M., aged 9½, had had scarlet fever at the age of 4, followed by tonsillectomy. The significant part of the history in this case is that in May, 1927, the patient had a sore throat, followed by polyarthritis. Soon after, she developed pleurisy and bronchitis. This continued for about two weeks, when she went to the Evanston Hospital. At this time, she had a slight systolic murmur and

¹⁴ This particular description was made from a section of a joint examined for us by Professor S. B. Wolbach.

signs of an indefinite process in the upper lobe of both lungs. Suspicion of tuberculosis was eliminated. Taken East for the summer, she developed progressive signs of a cardiac lesion, shortness of breath and the classic picture of severe endocarditis. Dr. Frank Spooner Churchill, from whom we received this case report, regarded the history as typical of one of rheumatic fever which ran a steady course with occasional remissions until death, six and a half months after the onset. Five different blood cultures taken a short time before death were negative. The temperature after admission to the Children's Hospital in Boston, though rarely higher than 100 or 101 F, occasionally reached 102 F, a short time before death it reached 103 F. Autopsy, which was performed by Dr. Shields Warren, showed an enormously enlarged heart, fibrinous pericarditis and only one small, grayish vegetation on the interior flap of the mitral valve. This was removed aseptically for culture. Other observations made at autopsy were consistent with the cardiac condition, and nothing relevant to this report was found except a few patches of bluish discoloration, which suggested to the pathologist either hemorrhage or early bronchial pneumonia.

A large number of cultures were taken from this case in which the heart's blood, pericardial fluid, myocardium and heart valves were planted in three sets of mediums and incubated aerobically, under carbon dioxide, and in anaerobic jars. In all, twenty-three separate cultures were made. From the heart's blood, a pneumococcus was obtained which probably denoted a terminal infection and could be correlated with the bronchial pneumonic patches on the lungs. Of the other cultures, only two were positive. One was a flask of broth containing sterily removed pieces of myocardium and incubated under carbon dioxide, the other, a similar flask containing pericardial fluid. From both of these, an alpha streptococcus was obtained which grew out after three days. It was noteworthy that this organism was not present in the heart's blood, and escaped detection in five blood cultures taken before death. The pneumococcus may be explained by the fact that there were two or three small patches of congestion in the lung, which were regarded by the pathologist as possibly representing early bronchial pneumonic foci.

The streptococcus obtained in this case will be spoken of in further studies as streptococcus alpha, case 1.

CASE 2—W. H., a boy aged 9, was admitted to the Children's Hospital. Except for the present one, there was no history of illness, with the exception of measles. Three years previous to the time of admission he had had pain in the joints and some fever, and this had occurred almost every year since then. Eighteen months prior to admission, fever, nosebleed, pain in the left side and difficulty in breathing were present. Fever lasted ten days, but the patient was kept in bed for two or three months. He was reasonably well up to four weeks before admission. He then developed pain in the left knee, which subsided in a day, but he did not regain his ordinary vigor. About four weeks before admission, he developed increasing shortness of breath, nosebleed, pain in the left side and a temperature ranging between 101 and 102 F. He was admitted to the hospital with a fever of 103.6 F. Cough and expectoration, and a considerably enlarged heart with multiple murmurs were noted.

During his stay in the hospital, the temperature was continuously high, ranging about 101 F and occasionally reaching 105 F. A blood culture taken on this child at a time when the temperature was high revealed two types of streptococcus: atypical *viridans* of the alpha variety and a gamma strain of the type described by

Small in his studies This child was discharged improved several weeks after the blood culture was taken, the temperature having come down and the organisms having apparently disappeared from the blood

The organisms obtained from this case will be spoken of as streptococci, alpha and gamma, case 2

With the cooperation of Dr Breed of the House of the Good Samaritan, we have during the last two years taken careful blood cultures in a number of these cases during the febrile periods, always with negative results, and we have never, therefore, felt that we could definitely account for the fever During the past winter, we have had two further cases which came to autopsy and which seem to us to give a clue to this problem

CASE 3—E B, a girl, aged 13, had an unreliable early history About five years previous to the time of admission to the hospital, a school physician discovered a heart murmur Since that time she had been carefully supervised, and because of the condition of her heart had been restricted as to school hours and exercise She had had periodic attacks of fever since that time and had been compelled to go to bed occasionally for a week at a time This condition continued until two months before admission to the House of the Good Samaritan At this time she developed cough, swelling of the feet and other signs of cardiac decompensation This diagnosis was confirmed on physical examination at the hospital, where mitral regurgitation and stenosis, aortic regurgitation, auricular fibrillation with rapid ventricular rate, pulmonary edema, large liver and ascites were determined She died a few days after admission

Observations made at autopsy were typical of a case of this kind As far as the bearing on this report is concerned, it is important to note that there was in addition to the usual enlargement of the heart, considerable exudation into the pericardium, but no fresh vegetations were observed Cultures were taken of the pericardial fluid and the heart's blood In this case, a culture from the spleen was also taken, flamed bits of splenic tissues being planted in various mediums

The heart blood and pericardial fluid were sterile, but from one of the spleen flasks two types of nonhemolytic streptococci, one of the alpha *avidans* type, the other of the gamma type, were isolated

These organisms will be referred to as streptococci alpha and gamma, case 3

CASE 4—H M, a girl, aged 4, began to complain of stiffness and soreness of one leg and developed a stiff and swollen ankle a year previous to the time of admission All symptoms disappeared after the patient had remained in bed for a week Tonsillectomy was advised but was not performed After three weeks the patient began to develop pains in the joints rather more severe than those during the first attack, and at this time a cardiac lesion was determined Seven months ago, she was admitted to the hospital, where mitral stenosis and regurgitation were determined She remained in more or less the same condition, usual in cases of this kind, with considerable evidence of mechanical difficulty in the heart and a gradual aggravation of the disease Finally she developed an acute pericarditis with elevation of temperature, and died about eight months after admission Blood cultures were not taken during the course of her stay in the hospital

At postmortem examination, in addition to the greatly enlarged heart, there was fibrinous endocarditis, and there were a number of small vegetations on the mitral valve. With the exception of a considerably enlarged spleen and liver and the other congestive conditions secondary to the cardiac insufficiency, there were no lesions.

In this case also all cultures were sterile except the one taken from the spleen, and the relative sparseness of organisms in the spleen was apparent from the fact that nothing grew on plates smeared with cut sections of the spleen, and only one of the spleen flasks developed a nonhemolytic streptococcus of the alpha *viridans* type.

The last two cases indicate that in many of the cases of chronic rheumatic endocarditis, the focus of persistent infection may lie in the spleen, since in both cases the heart's blood and pericardial fluid were sterile under cultural conditions identical with those to which the material from the spleen was subjected.

In view of the many claims of specific organisms in cases of rheumatic endocarditis, the most recent ones by Small and Birkhaug, it is interesting to compare the various organisms obtained from these cases, so much alike in history and so typical of the rheumatic syndrome, in their bacteriologic and antigenic properties. The mere fact of our obtaining two distinct forms from two cases is in itself significant, and confirms the observations of Swift and his co-workers.

In view of the problem as to place of lodgment of the organisms in the period between acute attacks, case 1 is interesting in that the only positive culture obtained—apart from the obviously incidental pneumococcus—was from the myocardium. This is particularly significant in view of the observations of two of our former associates, Hopkins and Parker,¹⁵ who, in our laboratory in New York, studied the distribution of streptococci in rabbits fatally infected during the latent period between injection and the reappearance of organisms in the blood, during which—as Bull and others¹⁶ have shown—the injected organisms disappear. They found that during this period the bacteria seem to be protected to some extent from destruction in the muscles, whereas in other organs, such as lung, spleen and liver, they are being actively phagocytosed.

The next two cases are significant in a similar way, in that they tend to reveal the localization of the responsible organisms in children with obvious chronic endocarditis of rheumatic nature in which blood cultures are usually sterile. It is, of course, well known that children with chronically damaged hearts following rheumatism, after weeks or months of apparent well-being and normal temperature, may often develop slight fever, rising to 102 F° or even a little higher, during which there is an exacerbation of the general condition. Such periodic attacks are usually

¹⁵ Hopkins and Parker. J Exper Med **27** 1, 1918.

¹⁶ Bull. J Exper Med **24** 7 1916.

accompanied by leukocytosis and have been regarded as a possible lighting up of a latent focus of infection

The data in tables 1 and 2 illustrate the antigenic differences between the various organisms isolated from these four cases, as determined by agglutination. The figures show that each of the organisms agglutinated to a considerable strength in the serum of rabbits homologously

TABLE 1—*Limit of Agglutination in Serum of Rabbits Immunized with Streptococcus*

Organisms	Serum vs Strain α Case 1				Serum Strain γ Case 2		Serum Strain α Case 2	
	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8
Streptococcus alpha case 1	5120	5120	2560	2560	80	80	40	80
Streptococcus alpha case 2	320	320	160	320	80	160	2560	2560
Streptococcus gamma case 2	40	80	40	80	2560	2560	80	80
Streptococcus alpha case 3	40	40	40	40	40	40	40	40
Streptococcus gamma case 3	0	0	0	0	0	0	0	0
Streptococcus alpha case 4	0	0	0	0	0	0	0	0

TABLE 2—*Biologic Reactions*

Organisms	Dextrose	Lactose	Mannite	Saccharose	Saline	Inulin	Raffinose	Bile*
Streptococcus alpha case 1, myocardium strain	+	+	+	+	+	—	+	—
			48 hours				4 days	
Streptococcus alpha case 2	+	+	—	+	+	—	—	—
Streptococcus gamma case 2	+	+	—	+	+	± Slightly pink after 10 days	+	—
Streptococcus alpha case 3	+	+	+	+	+	Very pink after 24 hours + color disappeared gradually	+	—
Streptococcus gamma case 3	+	+	+	+	+	± Very slight pink after 10 days	+	—
Streptococcus alpha case 4	+	+	—	+	+	—	+	—

* In this table the plus sign indicates acid in twenty-four hours, the minus sign, negative, and the asterisk insoluble

immunized. While there was some group reaction, there was consistently feeble agglutination in heterologous serums, and with the strains gamma of case 3 and alpha of case 4 there was no agglutination in the serums produced with the other organisms.

Sugar fermentations also showed inconsistency, though less than agglutination, but it is noticeable that in case 3 there was considerable similarity in the sugar fermentations between the alpha strain and the gamma

We consider the agglutination heterogeneity the important point, since the work that is going on in our laboratory in the hands of Grinnell on the mutation of various streptococci has caused us to feel much uncertainty regarding the permanent fixity of such characteristics as action on blood

In our previous work on pneumococcus allergy, we believe that we obtained evidence that the antigen liberated by biologic lysis of bacteria in inflammatory foci was more potent for sensitization than the substances produced in vitro by chemical manipulation. This supposition is further borne out by the recent work of Duval,¹⁷ who found that when he injected hemolytic streptococci into the pleural cavities of homologously immunized rabbits the exudate, within three or four hours, contained substances more potent for skin reactions than the Dick toxin. This is pertinent to our problem in view of the opinions recently expressed by Dochez concerning the possible allergic nature of the scarlet fever reactions.

We repeated the Duval experiments with one of the alpha organisms, we injected a twenty-four hour, concentrated broth culture into the pleural cavity of an immune rabbit, and three hours later took out about 5 cc of pleural exudate. Films from this showed a great number of polymorphonuclear leukocytes, but no bacteria. This material was centrifugalized clear and found to give specific precipitation with a homologous serum which agglutinated in dilutions of 1:2,560. Injection of some of this material into the skin and in joints of a sensitized rabbit was suggestive, but not absolutely conclusive, however, the experiments all showed that, within the body of an immunized animal, bacterial substances are liberated, probably by lysis, in a concentration sufficient to give specific antigenic reactions.

SUMMARY

We have reported the cases described in this paper because they seemed to us to illustrate certain features in the bacteriology of rheumatic fever which were inconsistent with the assumption of a specific and single bacteriologic etiology in this disease. The cases were all of more or less the same clinical group, the organisms antigenically and in other respects differed from each other.

Moreover, the isolation of the bacteria in one case from the myocardium and in two—which illustrate the more chronic type of the disease—from the spleen, seems to us to offer a reasonable explanation for the frequent absence of these organisms from the blood stream and to point to the probable localization of the bacteria during the prolonged periods of quiescence. This also indicates the places from which cultures

17 Duval and Hubbard. *J Exper Med* 46:379, 1927.

at autopsy may be expected to yield the streptococci when they are absent from the blood and the pericardial exudate

Moreover, a coordination of the observations in these cases with our prolonged experimental studies on bacterial allergy seems to us to lend added support to the point of view that focal infection with a consequent sensitization of the body is in keeping with the many otherwise contradictory experimental and clinical observations that have been made on this disease, and to lend added weight to the view that the allergic theory is a reasonable one as applied to the causation of many of the manifestations of rheumatic fever

We have not yet been able in our experimental work to produce joint lesions in allergic animals except by direct injection of the antigen into the joints. All attempts to arouse sterile joint reactions in either allergic rabbits or guinea-pigs by injecting the antigen intravenously or intraperitoneally have so far failed, although we have been attempting this for a number of years. Indeed, we have found that success in producing joint manifestations of any severity have usually necessitated repeated injections of the same joints

The experimental circle of evidence, therefore, is not entirely closed, but it may be that in man the frequent association of joint manifestations with chilling, exposure, etc., may be due to the establishment thereby of abnormal circulatory communication between joints and the blood stream, in which sensitizing contact between the constituents of the blood stream and the joints can take place in a focally infected allergic person

It seems to us possible that the curious frequency with which non-hemolytic streptococci are associated with the disease, while at the same time the nonhemolytic streptococci so found represent many varieties, may be due to the fact that with these organisms that peculiar balance between invasiveness and resistance is established in man, which most easily results in chronic infection

At the same time, in appraising the significance of the different varieties of organism which Swift and his co-workers, as well as we ourselves, have found in one and the same case, we must remember that studies on bacterial mutation are considerably altering our opinions concerning the fixity of species, and modifications of the organisms inhabiting the body for months and years must be considered as possibilities until this chapter of bacteriology has made further progress

The suggestion that many of the manifestations of rheumatic fever are dependent on the mechanism of bacterial hypersensitiveness is not a new one, but has been gaining force. On the whole, our observations of the last four or five years, both in the experimental study of bacterial allergy and in the analysis of clinical material, incline us to favor this view rather than that favored by Small, Birkhaug and others in which a single specific toxin-forming organism is held responsible

Book Reviews

IMMUNITY IN SYPHILIS By ALAN CHESNEY, M.D., Johns Hopkins Medical School Medicine monograph 12 Price, \$2.50 Pp 85 Baltimore Williams & Wilkins Company

The nature of syphilis is such that every specialty in medicine, including public health, is vitally interested in advances made in the study of this disease. The literature on syphilis is scattered in the medical journals of every specialty of every country. On this account, it is especially gratifying to note that the important contributions bearing on immunity in syphilis have been brought together in monograph form by Dr. Chesney in a very readable book of about eighty pages.

It is recommended that clinicians and laboratory workers interested in this subject should read the book from cover to cover. Those who cannot do this, will find a complete general summary in a few pages given at the end of the monograph, where the present status of this important problem is tersely presented.

Some of the most significant and pointed of the author's remarks are as follows. Man, monkey, rabbit and guinea-pig are the only animal species now known to be susceptible to infection with *Spirochaeta pallida*. Nothing is known as to individual immunity in syphilis, and no race of man appears to be insusceptible. Second attacks of syphilis in the same person are extremely rare. Syphilitic persons gradually acquire a resistance against the virus introduced into the skin. This resistance, however, is only relative and is more pronounced during the later stages of the disease.

Experimentally, monkeys and rabbits acquire a resistance to a second infection after a certain period of time. Rabbits may acquire, during the course of syphilis, an immunity which will proceed after the infection has been abolished. Experiments with rabbits also show that immunity which develops in these animals during the course of syphilitic infections, is more effective against a second inoculation with homologous strains than with heterologous strains.

Attempts to produce in man or other animals active immunity to syphilitic infection by using syphilitic tissue, cultures of spirochetes, living or dead, syphilitic virus or their products have been uniformly unsuccessful, provided the disease itself was not produced. Also attempts to confer immunity to syphilis by passive transfer of serum have likewise been fruitless. Infection with virulent virus seems necessary to produce immunity.

Antibodies such as agglutinins, precipitins and similar substances have been observed in the serum of animals following immunization, especially with the cultures. Such bodies have also been observed in the serum of patients with syphilis, but it is not at all certain that such substances have anything to do with natural or acquired immunity in this disease.

The immunity mechanism in syphilis is not at all clearly understood. Antibodies circulating in the blood do not appear responsible for acquired resistance. The facts would seem to point to the cells as being of prime importance in the resistance mechanism. It seems certain that the tissues of the syphilitic person have the capacity to react to new syphilitic virus in a way wholly different from that manifested by the normal person. Spontaneous sterilizing immunity in syphilis, if it ever occurs, must be extremely rare.

Man, as a rule, is incapable of eliminating syphilitic infection from his body unaided, though he does possess the ability to react and to limit somewhat its extent. This reaction is incomplete, however, though effective for a long time. Its incompleteness may be due in part to an immunization on the part of the invading organism against the host, so that a mutual adjustment, as it were, proceeds whereby a state of ideal parasitism is approximated.

A valuable bibliography containing the most important references to this subject is appended.

TRABAJOS Y PUBLICACIONES DE LA CLINICA DEL PROFESSOR PEDRO ESCUDERO
By EDMUND ANDREWS Volume 2 Price, \$12 00 Buenos Aires El Ateneo,
Florida 371, 1926

This second volume of the publications of Escudero's clinic contains forty-nine articles. The caliber of the work is easily up to the high standard of the first volume, and the reviewer regrets that the material of our South American colleagues cannot be made available to speakers of English as ours is to them in the Spanish Edition of the *Journal of the American Medical Association*.

Owing to lack of space only a few of the important communications are mentioned in this review.

Much of the volume is taken up with careful studies on the value of the high-fat diet in diabetes. This series of articles, mostly by Escudero himself, is an accurate and painstaking analysis of many cases in which the Allen method of treatment is used. The results of these studies are favorable.

Another interesting set of reports is that concerning the series of biopsies of bone marrow made in cases of various blood dyscrasias. The procedure is simple and safe. An incision through the skin and periosteum 0.5 cm long is made over the head of the tibia under local anesthesia, and a small hole drilled into the medulla. An anesthetic is not needed for this stage. Smears of the exuded marrow give a much exaggerated picture of the conditions found in the blood and the characteristic cells are found at an earlier stage in the disease. The authors are led to conclude that this is an important adjunct in the diagnosis of many diseases of the blood.

Another interesting feature is the study of eleven cases of gastric ulcer cured by cholecystgastrostomy. The condition in all the patients had endured for many years since the operation. All the patients were clinically well. Radiological examinations did not give any indication of ulceration, and no complications of any sorts had arisen. Chemical analysis showed that the degree of acid in the stomach had been markedly lessened.

Escudero's test for latent diabetes as used by him in certain diseases of the skin and the eyes, etc., appears to have a real value. He says (p. 394) "It appears then that in a healthy individual, a great quantity of carbohydrate ingested in a short time produces a stimulation of the activity of the pancreas bringing about a state of hypersecretion. This state of hypersecretion is sufficiently sustained so that at the end of 3 hours, not only has the excess of sugar incorporated in the blood been made to disappear, but also the blood sugar has been lowered to a point below that at the beginning of the experiment." Finding a blood sugar level higher than before is indicative of a latent diabetes. Utilization of this test has revealed latent diabetes in a number of cases and excellent clinical results have come about from antidiabetic therapy in such cases.

ELEMENTS OF PHYSIOLOGY FOR STUDENTS OF MEDICINE AND ADVANCED BIOLOGY. By ERNEST G. MARTIN, PH.D., Professor of Physiology in Stanford University, California, and FRANK W. WEYMOUTH, Associate Professor of Physiology in Stanford University, California. Price, \$8.00. Pp. 784, with index and 133 illustrations. Philadelphia: Lea & Febiger, 1928.

This is on the whole a well written textbook of physiology intended for graduate and medical students. Dr. Martin, senior author, is known not only for his many important researches in physiology but also for his revision of the old classic, Martin's "Human Body." The subject of physiology is treated under four main headings.

Part 1, the nature and capacities of protoplasm, is written by Dr. Martin. There are nine chapters of 154 pages which deal with cell organization, cell membranes, chemistry of life processes, conduction, reflex action and gland function.

Part 2 also written by Dr. Martin, has as a general heading cell environment. It consists of five chapters, on regulation of neutrality, on inorganic salts, vitamins, hormones and oxygen.

Part 3, by Dr Martin, under the heading, body maintenance, includes fifteen chapters, dealing mainly with the physiology of the blood, circulation, respiration, digestion, secretion and metabolism

Part 4, termed external adjustment contains twelve chapters, most of them written by Dr Weymouth. This section deals with the nervous system and sense organs, with a final chapter on reproduction

There is some unavoidable repetition because of the arrangement of the material. Despite this the book is on the whole concise and as critical and accurate as one can expect where the whole complex subject of physiology is treated by two men

One is told in the preface that the authors had two "key-principles" in mind in preparing the book. The first is to present the essential groundwork of general physiology applicable to all living things, the second is that every protoplasmic cell is inherently a cell sustaining system. One can readily see the importance of the first so-called key-principle, but the importance of the second principle in the preparation of a textbook as a guide to graduate and medical students is not so clear, at least in the present status of the science of physiology. Nevertheless, the book will undoubtedly take its place with the best in the field today

HANDBUCH DER INNEREN MEDIZIN HERAUSGEGEBEN VON G V BERGMANN
und R. STAEHELIN IV. BAND I. THEIL BLUT, BEWEGUNGSAPPARAT,
KONSTITUTION, STOFFWECHSEL VON L. MOHR und R. STAEHELIN
Second edition Berlin Julius Springer, 1926

For many years the public has waited for the new edition of the "Handbuch der inneren Medizin von L. Mohr und R. Staehelin" which during the most important period of the development of modern medicine in Germany was probably a "Handbuch" rather unique in its completeness and thoroughness. The enormous demand which the new edition by G v. Bergmann and Staehelin encountered abroad is the best proof of the value of this encyclopedia of internal medicine.

The fourth volume, first part, which is the subject of this review, discusses the Blut, Bewegungsapparat, Konstitution, Stoffwechsel, Blutdrusen, Erkrankungen aus physikalischen Ursachen, Vergiftungen. The men who have contributed to this volume are W. Alvens, M. Cloetta, G. Denecke, R. Doerr, W. Falta, E. St. Faust, E. Hübener, M. Klotz, L. Lichtwitz, F. Lommel, M. Lüdin, Erich Meyer, P. Morawitz, R. Staehelin, E. Steinitz, R. von den Velden and H. Zangger. The names of several of these scientists are well known also in this country. The most surprising and important fact for the reader is how concise this work is and how each of these men figures as a functional part for the integration of an entity. As of especial interest for the American reader, I wish to point out the chapter about the clinical constitution by R. von den Velden, "The Diseases of the Blood and the Hemogenetic Tissues" by P. Morawitz and G. Denecke, and that on metabolic diseases by L. Lichtwitz. No well proved fact and no important theory are missed by those authors. The bibliography is, one may say, complete. The publisher, Julius Springer, Berlin, is to be congratulated on the excellence of the edition. This encyclopedia of internal medicine will be of great value for scientists, teachers and students. It should be a part of every scientific library.

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TAPEWORM ANEMIA

THERAPEUTIC OBSERVATIONS ^{*}

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CYRUS C STURGIS, M D

AND

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The cause of the anemia which appears in a small percentage of persons harboring *Dibothryocephalus latus* (*Diphyllobothrium latum*) has not received, as yet, an adequate explanation. Ehrstrom ¹ estimated that in Finland, where from 250,000 to 275,000 inhabitants are *Dibothryocephalus* hosts, only from 0.1 to 0.5 per cent of those infected with the tapeworm develop anemia. A correspondingly small percentage was noted in other countries. Ehrstrom pointed out that anemia may appear in a small, but relatively almost as frequent a, percentage of patients infected with *Taenia saginata*, *T. solium* and *Ascaris lumbricoides*. Piney, ² among others, noting its close resemblance to pernicious anemia, suggested that it may be a form of this type of anemia which has been elicited in susceptible persons by the toxins of the tapeworms. A constitutional predisposition plus the stimulus given by the tapeworm gives rise, in the host, to symptoms and signs which are frequently indistinguishable from those of pernicious anemia in noninfected persons. Schauman ³ noted relapses in some patients many years after the expulsion of the parasites, even in the absence of reinfection. He also noted true pernicious anemia in relatives of patients with anemia who were infested. It has been suggested that the tapeworms may be macerated or otherwise abnormal in those who developed anemia, and that the intact and healthy tapeworm is not harmful to the host in this respect. This observation, however, has not been confirmed in all cases. Schau-

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1 Ehrstrom, Robert. Zur Frage des gastrointestinalen Ursprungs der perniziösen Anämie, Ztschr. f. klin. Med. **105** 106, 1927.

2 Piney, A. Recent Advances in Haematology, Philadelphia, P. Blakiston's Son & Co., 1927, p. 71.

3 Schauman, O., quoted from Piney (footnote 2, p. 71).

man and Tallqvist⁴ and others⁵ have found that the proglottids of the tapeworm may contain 10 per cent (of solids) of cholesterol oleate. This substance, while hemolytic in vitro, is apparently not effective on parenteral injection. The ground up bodies of the tapeworms, however, exert a hemolytic action both in the test tube and in the body. The active substance is alcohol soluble and is bound to the tissues but not to the lipoids (Syderhelm⁶). The presence of a hemolytic substance in the tapeworm does not account, however, for the differences in reaction of the hosts.

The resemblance of the blood picture to that of pernicious anemia suggests that a similar mechanism affecting the hemopoietic system may be present in both diseases. As Minot and Murphy⁷ had shown that the blood of patients with pernicious anemia could be restored to normal when $\frac{1}{2}$ pound (227 Gm.) of liver was eaten daily, this regimen was tried on a patient having a marked anemia and *Dibothryocephalus latus* infection.

REPORT OF CASE

The patient was a well developed, obese, white woman, aged 53. She was born in Russia (Lithuania), but at the age of 10 years came to America and lived in Detroit. Her father was living and well at the age of 70, but her mother had died of pernicious anemia two years previous to the patient's admission to the hospital. The physician who treated the mother reported that she had had "an undoubted case of pernicious anemia, with typical blood picture, cord symptoms, palpable spleen and occasional petechiae. The stools were negative for blood and ova."⁸ Three sisters and three brothers, as well as the husband, did not show signs of anemia. The patient had been married for thirty years and had had ten children. One died at birth following a "dry labor," and one at the age of 7 months of pneumonia. She had not had any miscarriages. After the tenth pregnancy a "laparotomy with sterilization" was performed, resulting in an artificial menopause. The only previous illness of note was an attack of "bronchitis" about three years previous to the present admission. She was then confined to her bed for three weeks.

The chief complaint during the present illness was "weakness." This had started insidiously about two years previously, with loss of appetite and increased nervous irritability. About five months before admission, the fatigue and weakness became more marked and the patient noted some numbness of her fingers. She also noted that her feet were dragging and that she could not walk as well as previously. Apparently there was no change in sensation, except that the lower extremities felt heavy. Later, she had a moderate diarrhea which lasted three

4 Schauman, O., and Tallqvist, T. W. Ueber die blutkörperchenauflösenden Eigenschaften des breiten Bandwurms, *Deutsche med. Wchnschr.* **24** 312, 1898.

5 Tallqvist, T. W. Zur Pathogenese der perniziösen Anämie, mit besonderer Berücksichtigung der Bothriocephalusanämie, *Ztschr. f. klin. Med.* **61** 427, 1907.

6 Syderhelm, R. Zur Pathogenese der perniziösen Anämien, *Deutsches Arch. f. klin. Med.* **126** 95, 1918.

7 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87** 470 (Aug. 14) 1926.

8 Maver, W. D. Personal communication to the author.

or four days. This disappeared spontaneously, but some epigastric distress with gaseous distention and a tendency to belch remained. During the month preceding this she had noticed a sore tongue. "Blisters" appeared on her lips and tongue, and the latter was reddened. Her gums were frequently swollen, but she attributed this to irritation from her false teeth.

About two years before the present examination, the patient noted two lengths of a flat tapeworm, one about 2 feet (60.9 cm) long. She never noticed any more after that. The source of the infection is not clear. The patient was always fond of fish, having been in the habit of eating white fish, perch or pike at least twice a week. Little meat or vegetables were eaten. Other members of the family did not show evidence of infestation, and eggs were not found in their stools.

The outstanding features on physical examination were the intense yellowish pallor of the skin and mucous membranes. The hair and the iris of the eyes were dark brown. The fundi did not show evidence of hemorrhages. The tongue was smoother than normal but was not atrophied. A large abdominal hernia was present at the region of a medial scar from the laparotomy. The heart appeared normal. The systolic blood pressure was 135, diastolic, 70. The lungs showed

TABLE 1—*Differential Leukocyte Count*

	Per Cent		Per Cent
Polymorphonuclear neutrophils, adult	29.5	Mycoblasts	1.5
Polymorphonuclear neutrophils, young	6.0	Small lymphocytes	20.5
Polymorphonuclear eosinophils	1.0	Large lymphocytes	25.5
Polymorphonuclear basophils	0.5	Monocytes	2.0
Myelocytes	1.0	Crushed cells	7.5
Metamyelocytes	4.0	Hemohistioblasts	1.0

TABLE 2—*Measurements of Red Blood Cells*

	Per Cent		Per Cent
3.75 microns	1.5	9.00 microns	21.5
4.50 microns	3.5	9.75 microns	10.5
5.25 microns	2.5	10.5 microns	2.5
6.00 microns	5.5	11.25 microns	2.0
6.75 microns	9.5	12.0 microns	1.5
7.50 microns	18.5	12.75 microns	0.5
8.25 microns	20.5		

evidence of a mild bronchitis. The spleen was not palpable, but the edge of the liver was soft and palpable 8 cm below the costal margin. The reflexes were slightly more active than normal, and the vibration sense was within normal limits. Her best weight had been 150 pounds (68 Kg) seven years previously. She had lost weight during the latter part of the illness, so that when she presented herself at the hospital she weighed 117½ pounds (53.3 Kg).

The temperature during the first eight days in the hospital ranged from 99 to 102 F, being lower in the morning and higher in the evening and reaching normal on the fifth day after the administration of liver was begun and remaining normal thereafter. Free hydrochloric acid was not found in the fasting gastric contents or in three successive fractions taken at half hour intervals after a gastric test meal. Blood was not found in the gastric contents. The stools showed many eggs of *Dibothryocephalus* (*Diphyllobothrium*) *latus*, but blood was not found. The blood count on admission showed 1,940,000 red blood cells per cubic millimeter, 6,600 white blood cells per cubic millimeter and 33 per cent hemoglobin (Sahli). The differential leukocyte count is shown in table 1.

The measurements of the cells on admission are shown in table 2.

The red blood cells were hyperchromic. There was 15 per cent of reticulocytes. Moderate poikilocytosis was present, and many of the large red blood cells were oval. There were 264 nucleated red blood cells per cubic millimeter. Most of the nucleated red blood cells were of macronormoblast type, but numerous megaloblasts were found. Stippled red blood cells and some with Howell-Jolly bodies, Cabot's rings and nuclear particles were present. Some of the large red blood cells were round or irregular, with uniform staining and an absence of a clearcut edge. Some of the microcytes were pale, and some were stippled. The platelets were slightly decreased in number.

In view of Macht's⁹ observation on the inhibitory effect of pernicious anemia serum on the growth of lupin seedlings in Shive's solution (prepared by mixing 104 cc of 0.5 molar solution of calcium nitrate, 30 cc of 0.5 molar solution of magnesium sulphate, and 36 cc of 0.5 molar monopotassium acid phosphate with distilled water sufficient to make 1 liter) the serum of the patient was tested on

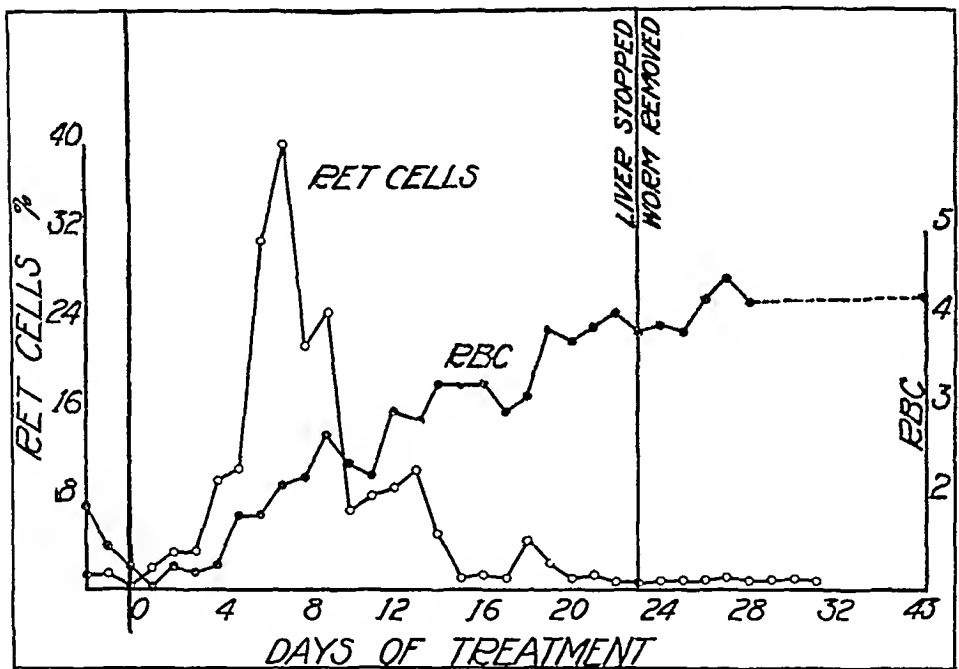


Fig 1—Graph showing changes in the red blood cell count and reticulocyte percentage during the course of treatment

two occasions, one before the tapeworm was removed and when the red blood cell count was 1,220,000 per cubic millimeter, and the other after the removal of the worm and when the red blood cell count was 4,210,000 per cubic millimeter. On the first occasion the growth was 60 per cent of that of the control, and on the second occasion the growth was 75.2 per cent of the growth of the control in twenty-four hours. There was definite inhibition of growth by the serum taken from the patient before the treatment with liver was started, commensurate with that which Macht outlined for the blood of persons with pernicious anemia.

The bile indexes and quantitative bilirubin (van den Bergh) readings are given in table 3.

The patient was treated with $\frac{1}{2}$ pound of raw, finely ground, calf's liver daily, and during this time antihelminthic medication was not given. Her blood responded just as that of a patient with typical pernicious anemia, with a rise in

⁹ Macht, D. I. Etiology, Diagnosis and Treatment of Pernicious Anemia, J. A. M. A. 89:753 (Sept. 3) 1927.

the reticulocyte percentage to 39 per cent, followed by a return to almost normal, and then a second rise to 11.6 per cent. The hemoglobin percentage rose steadily, and there was a definite rise in the red blood cell count. When the blood count was approaching normal (on November 4, fig 1), the patient received six doses of 1 cc each of oleoresin of aspidium in capsules while fasting, after a preliminary

TABLE 3—Data of Bile Index and Bilirubin Readings

	Bile Index	Van den Berg (Indirect)
October 14	60	1.5 milligrams per cent
October 18	15	1.2 milligrams per cent
October 28	5	0.9 milligrams per cent
November 2	5	0.4 milligrams per cent

TABLE 4—Changes in Blood Counts with Progress of Disease

Date	Red Blood Cells (Millions per Cu Mm.)	White Blood Cells (per Cu Mm.)	Hemoglobin (per Cent)	Reticulated Red Blood Cells (per Cent)	Therapy
Oct 12	1.94	6,600	33	1.5	
Oct 13	1.45	3,800	33	1.7	
Oct 14				2.2	
Oct 15	1.31	5,850	28	0.6	Feeding of liver started
Oct 16	1.10	6,050	30	2.0	
Oct 17	1.29	4,400	28	3.3	
Oct 18	1.22	9,550	28	3.5	
Oct 19	1.32	14,750	28	11.8	
Oct 20			29	13.1	
Oct 21	1.81	8,700	34	31.4	
Oct 22	2.15	8,350	40	39.9	
Oct 23	2.37	6,400	41	20.7	
Oct 24	2.77	7,750	50	27.0	
Oct 25	2.43	5,750	50	7.2	
Oct 26	2.34	8,500	50	8.1	
Oct 27	3.06	8,050	50	9.0	
Oct 28	2.87	7,350	55	11.6	
Oct 29	3.28	8,850	53	5.4	
Oct 30	3.31	8,850	55	7.3	
Oct 31	3.30	8,400	54	1.0	
Nov 1	3.02	10,150	63	1.6	
Nov 2	3.21	9,500	64	1.5	
Nov 3	3.90	10,900	64	4.5	
Nov 4	3.71	10,550	63	2.4	Antihelminthic medication, tapeworms expelled, feeding of liver discontinued
Nov 5	3.93	10,700	68	1.0	
Nov 6	4.09	12,250	63	1.1	
Nov 7	3.65	11,300	62	0.7	
Nov 8	3.70	15,900	62	0.7	
Nov 9	3.63	10,800	63	0.8	
Nov 10	4.16	12,150	64	0.2	
Nov 11	4.49	11,050	63	1.0	
Nov 12	4.19	11,550	64	1.1	
Nov 13	4.30	11,650	66	0.7	
Nov 14	3.85	13,650	61	0.8	
Nov 15	4.21	11,250	65		
Nov 28	4.25	11,750	71	0.8	
Jan 10	4.96	7,450	70		
March 12	4.41	5,950	60		

treatment with magnesium sulphate. Two tapeworms of the *Dibothriocephalus latus* type were passed, one about 9 feet (274 cm.) long and the other about 12 feet (365.8 cm.) long, when measured under slight tension. One was pinkish gray, the other slightly yellower. Except for a few terminal segments which were macerated, the tapeworm appeared in good condition.

After the expulsion of the tapeworms, the eggs were no longer found in the stools. Ingestion of liver was discontinued, and a regular diet without liver or kidneys was prescribed. Improvement continued without interruption.

In order to determine the presence of toxin in *Dibothriocephalus latus* and the possibility of absorption of this toxin by the patient, 20 Gm of the tapeworm was ground in a mortar with 200 cc of physiologic sodium chloride solution until the tapeworm was entirely emulsified. This mixture was then placed in a bottle and shaken for fifteen minutes and filtered through filter paper and then through a Berkefeld filter. The filtrate was cultured aerobically and anaerobically to insure sterility, and when this was confirmed, 0.1 cc of the sterile filtrate was injected intradermally into the patient and also into a normal person.

The patient did not show at any time a wheal formation at the point of injection. She was therefore not sensitized cutaneously to the toxins or proteins of soluble nature in the tapeworm. At the end of eighteen hours, at the point of

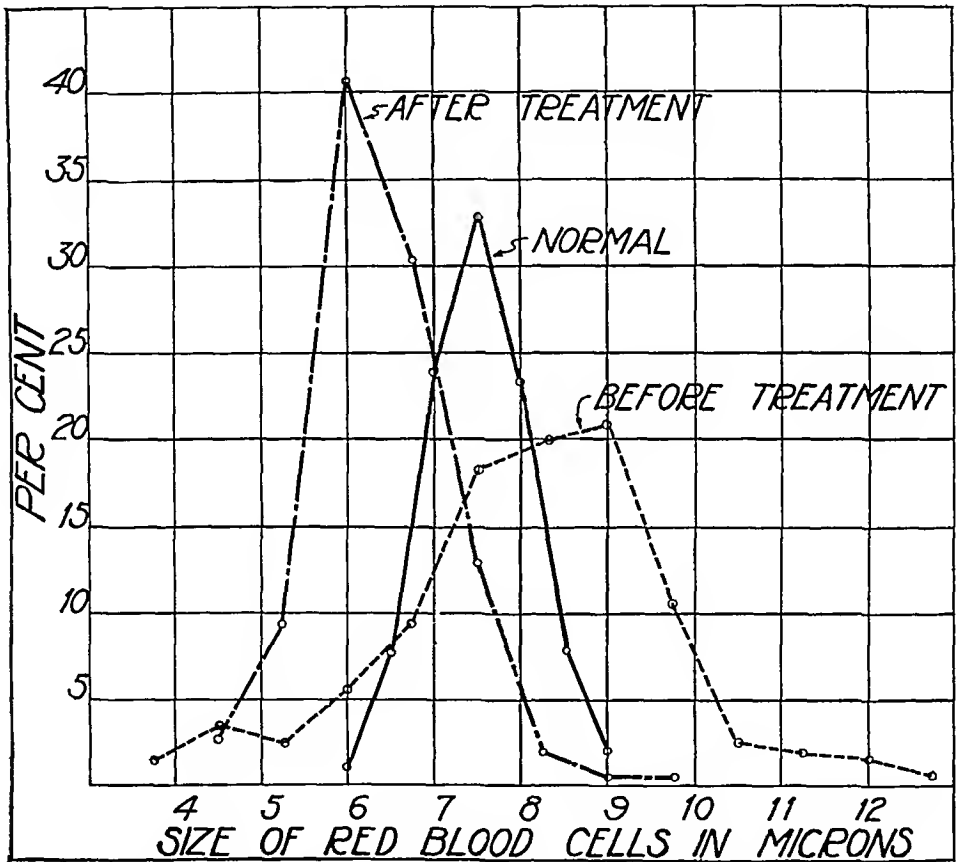


Fig 2—Graph showing the measurements of the red blood cells before and after treatment, in comparison with those of normal persons

injection, both the control and the patient showed a small area of erythema 1 cm in diameter. This demonstrated that there was little toxic material in the tapeworm substance and that the patient was not immunized to the small amount of toxin present. Presumably, therefore, she had not been absorbing toxic metabolic products from the parasite. The degree of toxin present is in no way comparable to that obtained from streptococci and other common organisms, because soluble filtrates from these organisms in 1:100 dilution produce large areas of erythema. The dilution of the tapeworm filtrate used was 1:10.

Table 4 shows the changes in the blood counts with the progress of the disease.

As the patient improved, the red cells approached normal in size and shape. A comparison of the size of the cells at the beginning of the treatment with those at the end of the treatment is shown in figure 2.

The patient's weight on discharge was 122 pounds (55.3 Kg). She appeared normal in all respects and was found to be perfectly healthy during five months of subsequent observation during which liver or kidneys were not eaten. She gained in weight and felt well. On March 12, 1928, five months after the patient was first examined, free hydrochloric acid was not found in the stomach contents one-half, one and one and a half hours after a gastric test meal.

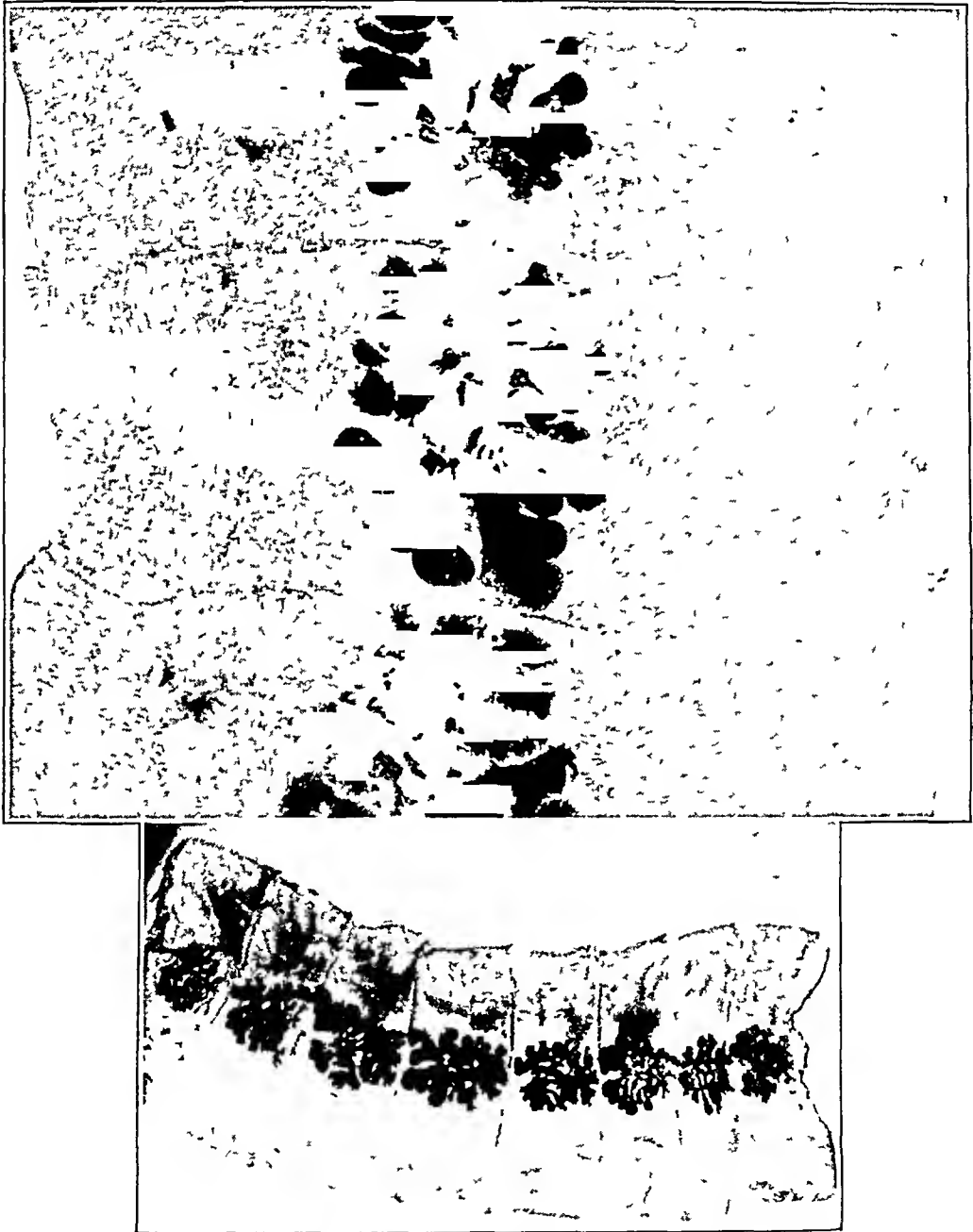


Fig 3—Segments of *Dibothryocephalus latus* (*Diphyllbothrium latum*) tapeworm injected with india ink to show the configuration of the uterus (Isaacs J Lab & Clin Med 7 691, 1922)

COMMENT

The interesting features of the case are the resemblance to pernicious anemia, as has been noted frequently in the literature, and the improvement in the blood picture on a therapeutic regimen for pernicious anemia.

The infection probably originated in Russia. The anemia usually disappears in this type of infection with the removal of the parasite, but in this case the anemia was decreased even when the parasites were still present. There is evidently some substance in liver which must counteract the anemia producing mechanism both in the addisonian as well as in this type of anemia. In both are found a macrocytic anemia (here 59 per cent of the red blood cells were 8.25 microns or larger), an increase in bilirubin, achlorhydria, fever and gastro-intestinal and neurologic symptoms with features that go with a deficiency in red blood corpuscles. In these respects the two diseases appear identical, lending some support to the concept that *Dibothriocephalus* infection is one of the possible mechanisms by which a pernicious anemia-like condition may be elicited in susceptible persons. The presence of pernicious anemia in the family (the mother) is confirmatory of this.

The relatively high icterus index and bilirubin content of the blood serum before treatment was started indicate that there was increased pigment metabolism, presumably from the hemolysis of red blood corpuscles. A possible hemolytic agent is found in the tapeworm, but there is apparently an additional factor necessary in the host before the material can be absorbed in amounts sufficient to cause marked destruction of red blood cells as so few of the carriers of the tapeworm develop anemia. The disease, however, does not appear to be primarily a hemolytic anemia. The presence of true megaloblasts in the peripheral blood stream and the increase in the number of reticulated red blood cells in the blood after liver feeding indicate that the bone marrow is in a state of hyperplasia with the bulk of the cells in an immature (nucleated) state. The leukopenia, accompanied by the presence of immature white blood cells as well as atypical and pathologic forms, is confirmatory of this, as this is the change that accompanies the malignant hyperplasia of immature erythroblastic tissue, as shown by Peabody and others. After recovery, the general "leukocyte picture" was more normal, although an occasional metamyelocyte was noted, as well as a pathologic lymphocyte. The lymphocyte count and percentage remained high (41.5 per cent on Jan. 10, 1928). Although one may expect an eosinophilia in an infection with tapeworm, the percentage did not increase in this case until after the feeding of liver was started. This may have been a "liver response" such as has been noted after feeding liver to patients with pernicious anemia by Watkins and Berglund¹¹ and by Whitby¹² and others. While the percentage of

10 Peabody, F. W. The Pathology of the Bone Marrow in Pernicious Anemia, *Am J Path* **3** 179, 1927.

11 Watkins, Charles H., and Berglund, Hilding. Analysis of Morphological Blood Changes in Pernicious Anemia Following Administration of Liver, *Proc Soc Exper Biol & Med* **25** 206, 1927.

12 Whitby, L. E. H. Leucocytic Changes Resulting from the Treatment of Pernicious Anemia with Liver, *Lancet* **214** 285, 1928.

eosinophils varied from 0 to 2.5 before the treatment with liver was started, it reached 5 per cent seven days later, 6 per cent in the second week and 8 per cent two months after removal of the tapeworm. As liver was not eaten during these two months, the persistent eosinophilia must have been related to some other factor.

The persistent achlorhydria resembles that of Addisonian pernicious anemia.

The liver diet was discontinued after the expulsion of the tapeworm in order that the further progress without the special diet could be noted. Improvement continued, as it usually does in such cases. It is possible, of course, that this case may have been one of true pernicious anemia with an incidental infection with tapeworm. Apparently all cases of *Dibothryocephalus* anemia are not as characteristic of the Addisonian type as this one.

SUMMARY

A case of *Dibothryocephalus latus* (*Diphyllobothrium latum*) anemia is described in which the blood picture, increase in bilirubin, achlorhydria, fever, neurologic and other clinical symptoms were indistinguishable from those of pernicious anemia. The patient's mother had died of pernicious anemia. It was found possible to cause a hematopoietic remission, with disappearance of the symptoms, by feeding liver daily, even though the parasite was not removed. Removal of the parasite, which was effected later by the administration of oleoresin of aspidium, accompanied the continuance of the convalescence. Evidence for the presence of soluble toxins was not obtainable from intradermal tests with saline suspensions of the tapeworm.

DANGER OF THE ADMINISTRATION OF EPHEDRINE IN HEART FAILURE ~

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AND

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While ephedrine has been employed in Chinese medicine for over five thousand years, it has been only in the past five years, since its reisolation and careful study by Chen and Schmidt, that modern medicine has added it to the list of drugs in daily use. In 1923, Chen called attention to ephedrine and conducted a careful study of its physiologic effect, so that in a short time the drug became popularized and freely used by practitioners of medicine and even by laymen.

At the present time, the drug is widely used for a variety of conditions, and the literature contains many interesting and instructive articles regarding its pharmacology, mode of action and therapeutic uses.

From time to time attention has been called to certain untoward effects from the use of this drug, and it is not considered amiss at this time to emphasize the point that this drug is not without danger, and that its indiscriminate use without a careful study of its mode of action and therapeutic limitations is to be condemned.

The chief action of ephedrine appears to be due to stimulation of the sympathetic nervous system, and the effects are similar to those of epinephrine. Ephedrine acts as a circulatory stimulant, largely due to its action on the cardiac accelerator mechanism, but if toxic doses are given, a fall in blood pressure and a depressor action on the heart muscle are noted. It appears to cause constriction of blood vessels supplied with vasoconstrictor nerves, more marked in the splanchnic area than in the limbs.

Other effects of ephedrine are inhibition and relaxation of intestinal muscles, stimulation of the uterine muscle and dilatation of bronchi and mydriasis.

Coincident with the rise in blood pressure, there is a definite increase in the cardiac rate, and occasionally various types of arrhythmia occur, particularly extrasystoles, and sometimes evidence of acute cardiac failure.

Ephedrine does not seem to be very toxic for certain animals, and the minimum fatal dose is from 100 to 145 mg per kilogram in rats.

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The drug is effectively absorbed from the intestines or may produce its effect following subcutaneous or intramuscular injection. Solutions are stable indefinitely and are not decomposed by boiling.

Ephedrine has been used as a circulatory stimulant in Addison's disease, and its efficiency as a bronchodilator has made it a valuable remedy in bronchial asthma. Its mydriatic effects are similar but more marked than those of cocaine.

Ephedrine has certain advantages over epinephrine in that its effects are more lasting, its solution is more stable and results may be secured when the drug is given by mouth. As a result, it has become a most popular drug, particularly in the treatment of patients with bronchial asthma and hay-fever and has replaced epinephrine in these conditions to a great extent. It is also used as a mydriatic and in spinal anesthesia as a useful agent in maintaining the blood pressure.

The fact that this drug is helpful in cases of asthma and hay-fever has become known to the layman, and as a result he frequently employs it without even consulting a physician. The sale of this drug is not surrounded by any restrictions, and it may be purchased by any one. This practice is to be deplored and may be actually dangerous for certain patients, particularly when the diagnosis of asthma is not definitely established and when cardiovascular disease may exist.

The most usually noted unfavorable symptoms have been sweating, tremor, cardiac irregularity, palpitation, general weakness and occasionally nausea and vomiting.

According to Middleton and Chen, the objective and subjective effects of ephedrine are tremor, a feeling of warmth, chilly sensations, nausea and dizziness. Others of less frequent or rare occurrence are tachycardia, restlessness, mydriasis, nervousness, headache, insomnia, dyspnea, a tired feeling and drowsiness. They noted that the time of the rise of systolic pressure after oral administration of this drug varies considerably, sometimes occurring within fifteen minutes and occasionally being delayed as long as 120 minutes, the average rise occurring in thirty-seven and a half minutes.

It seems to be the consensus of opinion that this drug is contraindicated in cases of cardiac insufficiency. Miller reported the occurrence of transitory pulsus alternans in a patient with myocardial degeneration following the use of ephedrine.

In the following case we observed signs of serious cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation after the use of ephedrine for a condition diagnosed as "asthma."

REPORT OF CASE

History—On Nov 14, 1927, E O L presented himself at the clinic of the United States Naval Medical School complaining of palpitation, which he first noted about November 7. He was perspiring freely, especially around the forehead, had a marked tremor of the fingers, complained of weakness of the muscles of the legs, shortness of breath and cough.

He had made a trip to the Orient in August, 1927. There was a history of hay-fever during the latter part of August, 1927, which disappeared in September. The patient also said that he had had attacks of hay-fever each fall for the past ten years. He said that he had been short of breath for several weeks, and that climbing stairs or even walking fast had caused dyspnea. On Oct 18, 1927, he drove to his camp in the mountains. On the day of his arrival in the mountains he felt fatigued, and that night he woke up with a feeling of marked breathlessness and a "smothering sensation." He felt it necessary to get out of bed and raise the window to seek relief. This attack lasted for several hours and was diagnosed by the attending physician as "asthma." Up to this time, he said that he had not noticed any irregularity of the heart, in fact, his attention had never been directed to the cardiac region. Following this acute attack, he was given some red capsules. He was informed that this was ephedrine. Following this attack, he was given forty $\frac{3}{8}$ gram (0.0243 Gm) capsules of ephedrine and told to take these as required for relief. He took the forty capsules during the following twenty days. At the end of this period, he came under our observation with the foregoing symptoms. He knew that his heart was beating rapidly, and that it was irregular at times.

At the time when the administration of ephedrine was begun and for the first few days thereafter, the patient felt fairly comfortable. The train of symptoms described was of gradual development, becoming progressively worse as the drug was continued.

Physical Examination—The height was 69 inches (175.3 cm), the weight, 205 pounds (93 Kg), the width of the chest, $39\frac{1}{2}$ inches (100.3 cm), and of the waist at the umbilicus, 49 inches (124.5 cm). The patient was cyanotic and was using the accessory respiratory muscles, the tonsils were rather large and showed evidence of infection, the gums were retracted around the posterior molars, and the upper molars showed extensive fillings. The eyegrounds showed slightly tortuous arteries and the disks were normal. Râles were heard at the bases of both lungs, and there was markedly impaired resonance over the base of the right lung posteriorly. The heart beat was rapid, the rate being 160 beats a minute, and the sounds were suggestive of gallop rhythm. The percussion measurements were as follows: The distance from the midline to the left border in the fifth interspace was 14 cm, the distance from the midline to the right border in the fourth interspace was 4.5 cm. The blood pressure was systolic, 110, diastolic, 80. There was a definite pulsus alternans.

The x-ray picture of the chest taken at a distance of 2 meters shows a dilated, decompensated heart and an effusion at the right base extending upward to the sixth rib (fig 1). The prominence of the lung markings indicate pulmonary congestion. The cardiac measurements were as follows: The distance from the midline to the left border in the fifth interspace was 15 cm, the distance from the midline to the right border in the fourth interspace was 4.5 cm. The transverse diameter of the heart was 19.5 cm and the transverse diameter of the chest 30 cm. This plate was taken at the time of the first examination.

Figure 2 shows the electrocardiogram taken on the same day. It indicates a cardiac rate of 160 beats a minute and shows the tachycardia to be of nodal origin. The blood picture was normal, the urine showed a specific gravity of 1.032 and albumin.

The administration of ephedrine was discontinued, the patient was put to bed, and tincture of digitalis was administered by mouth in doses of 1 cc four times a day. The dosage was reduced to 1 cc three times a day at the end of eight days, and was finally discontinued as the patient showed evidence of digitalization.

The cardiac rate gradually slowed, and the acute symptoms subsided. The patient, however, continued to show pulsus alternans for the following three weeks.



Fig 1—Dilated, decompensated heart with effusion on the right side of the chest (plate taken after the patient had continued the use of ephedrine for twenty days)

On December 3, the electrocardiogram (fig 3) showed a cardiac rate of 110 beats a minute, a normal rhythm and a left-sided preponderance. The T waves were inverted as a result of the administration of digitalis. It is of particular interest to compare this electrocardiogram with that in figure 2, noting that the P wave has resumed its normal position, that the amplitude of the QRS complex has been increased and that a definite left-sided preponderance is apparent.

The patient continued to show steady clinical improvement. On Dec 10, 1927, an x-ray picture of the chest (fig 4) taken at a distance of 2 meters showed that the effusion had entirely disappeared from the right side of the chest. The fields at the bases of the lungs had resumed their normal appearance, and the shadow of the heart showed a return toward normal. The cardiac measurements were as follows: The distance from the midline to the left border in the fifth inter-

space was 12.5 cm, the distance from the midline to the right border in the fourth interspace was 4.5 cm, the transverse diameter of the heart was 17 cm and the transverse diameter of chest 30 cm

The electrocardiogram taken at this time (fig 5) showed a cardiac rate of 88. The T waves showed definite inversion in all leads, indicating digitalization. The patient was somewhat nauseated on this day, and the administration of digitalis

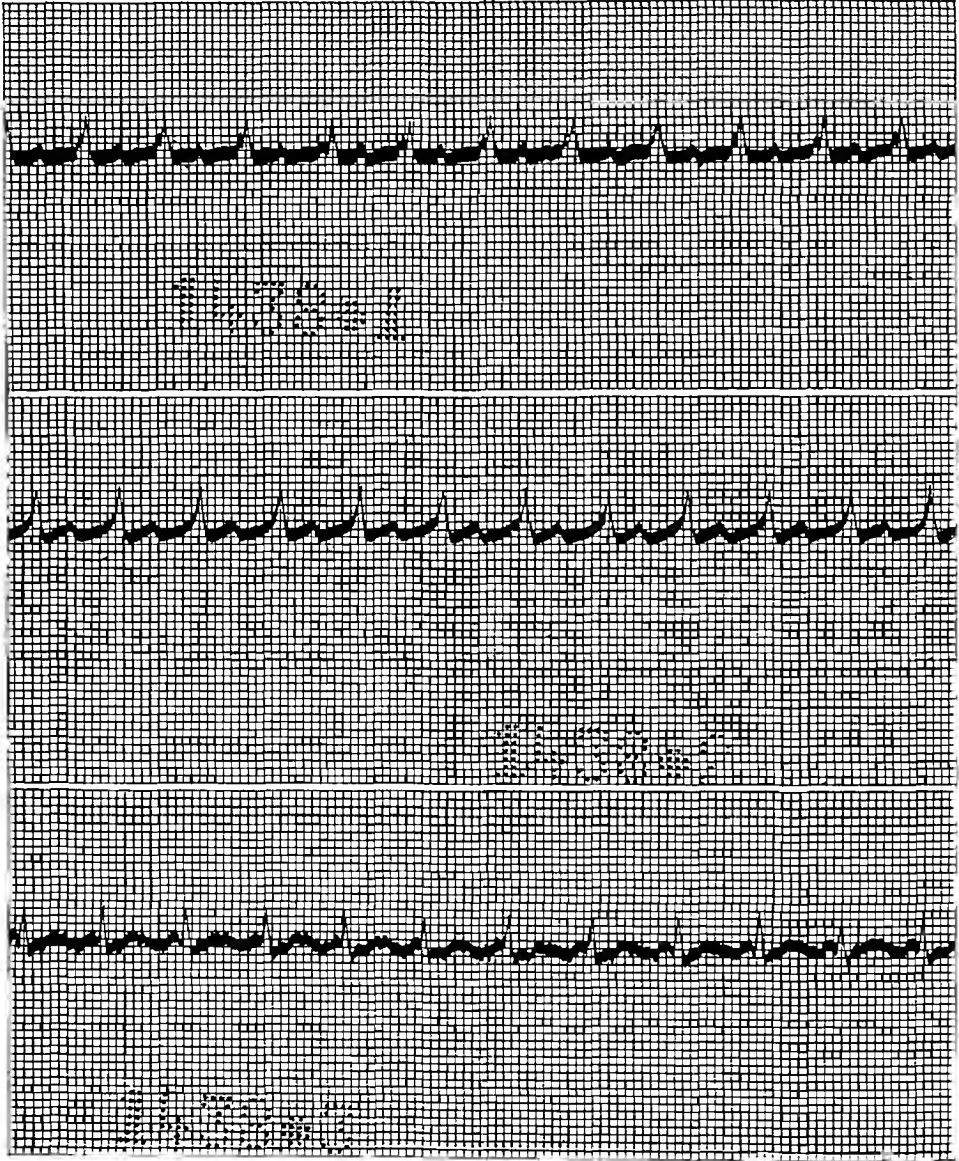


Fig 2—Electrocardiogram taken same day as the x-ray of the heart shown in figure 1, nodal tachycardia, with cardiac rate of 160 beats a minute

was discontinued. The rhythm was normal, and the amplitude of the QRS complex had still further increased. The evidence of left-sided preponderance was more marked, and cardiac compensation was well established. The patient was up and about and showed none of the distressing subjective symptoms noted at the outset. The urine showed a specific gravity of 1.022 and no albumin, sugar or casts.

Examination following the patient's convalescence revealed signs of myocardial damage as evidenced by cardiac hypertrophy and lessened cardiac reserve. He continued to show shortness of breath on exertion, and following an active day invariably exhibited some edema of the ankles, so that it was necessary to keep his activities within the range of his cardiac reserve power.

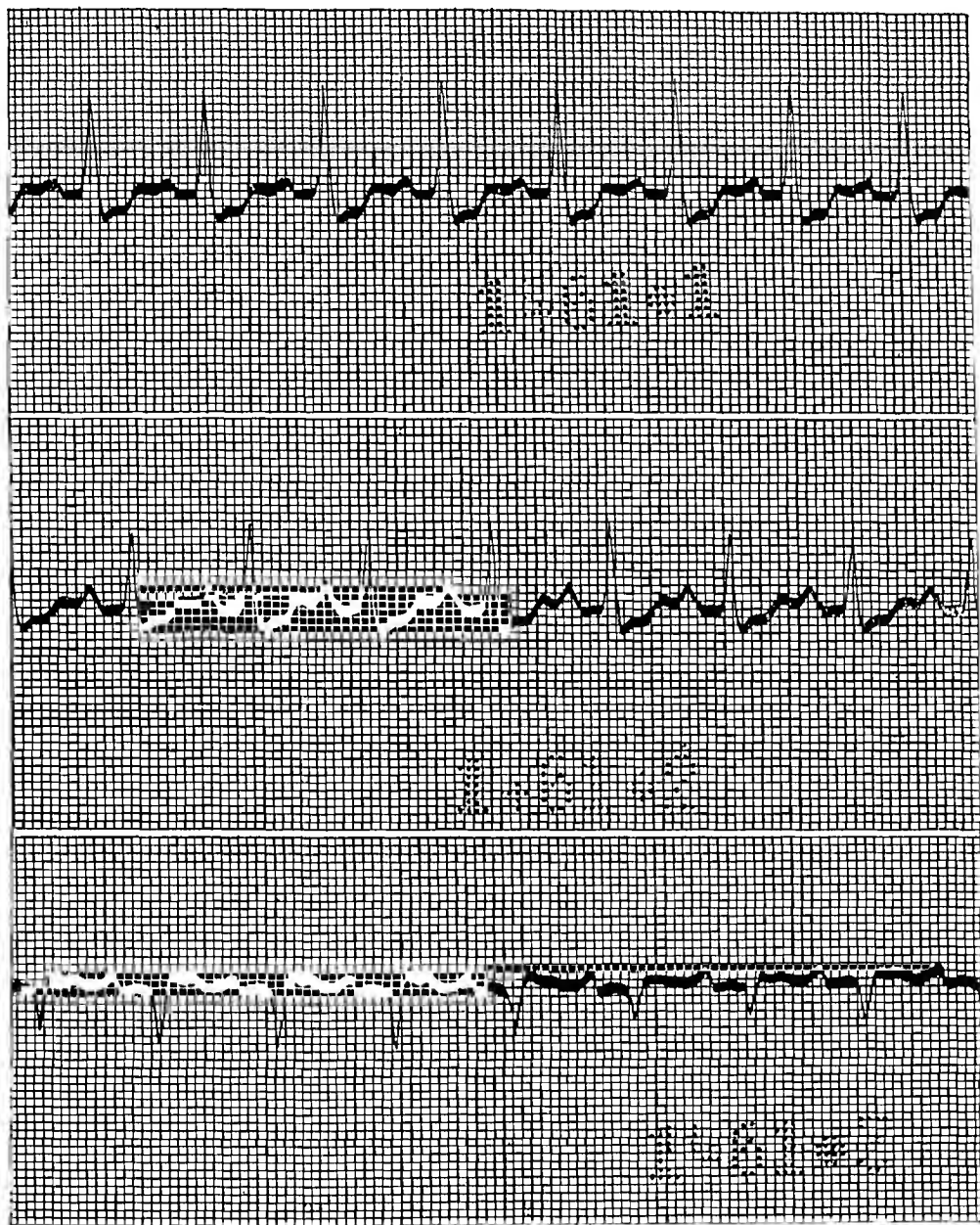


Fig 3—Electrocardiogram showing cardiac rate of 110 beats a minute, normal rhythm, left sided preponderance, inversion of T waves indicative of the effect of digitalis

It was considered advisable to begin again the use of digitalis in moderate doses in order to maintain the cardiac reserve.

The patient was kept under close observation in order to detect evidence of asthma, and he did not exhibit any evidence of this condition or any signs or

symptoms of nodal tachycardia. There was no return of palpitation, sweating, tremors or any of the phenomena noted at the outset.

Pulsus alternans disappeared following the return of cardiac compensation.

It may be of interest to note that, as is usually the case, the electrocardiogram gave no indication of pulsus alternans at any time during the course of the disease, although this phenomenon was easily demonstrated by the sphygmomanometer.

It appears to be well demonstrated that the patient did not have bronchial asthma. There was no eosinophilia, and there was only a single paroxysm of dyspnea which occurred at night following a

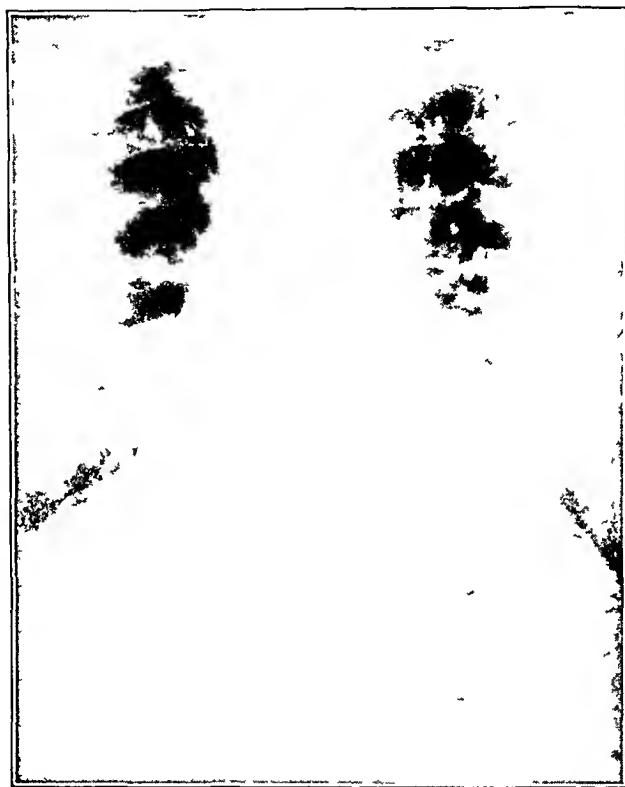


Fig 4.—Twenty-six days after beginning digitalis medication and discontinuance of ephedrine, the lung fields have resumed a normal appearance and the cardiac shadow shows a return toward normal.

fatiguing day. There had been evidence of a failing myocardium for several weeks preceding this attack, and there had been no return of any symptoms suggesting bronchial asthma either during convalescence or following recovery. The clinical course and marked improvement under rest and digitalis therapy would seem sufficient to establish the diagnosis of cardiac failure.

SUMMARY AND CONCLUSIONS

A clinical case is presented in which the diagnosis of asthma had been made following an acute attack of dyspnea coming on at night after

a long, fatiguing trip. The patient had been given ephedrine, $\frac{3}{8}$ grains, and took forty doses during a period of twenty days, a total of 15 grains (0.972 Gm). Following the administration of this drug, he developed evidence of acute cardiac decompensation accompanied by marked dyspnea, sweating, tremors, weakness and palpitation. He developed a

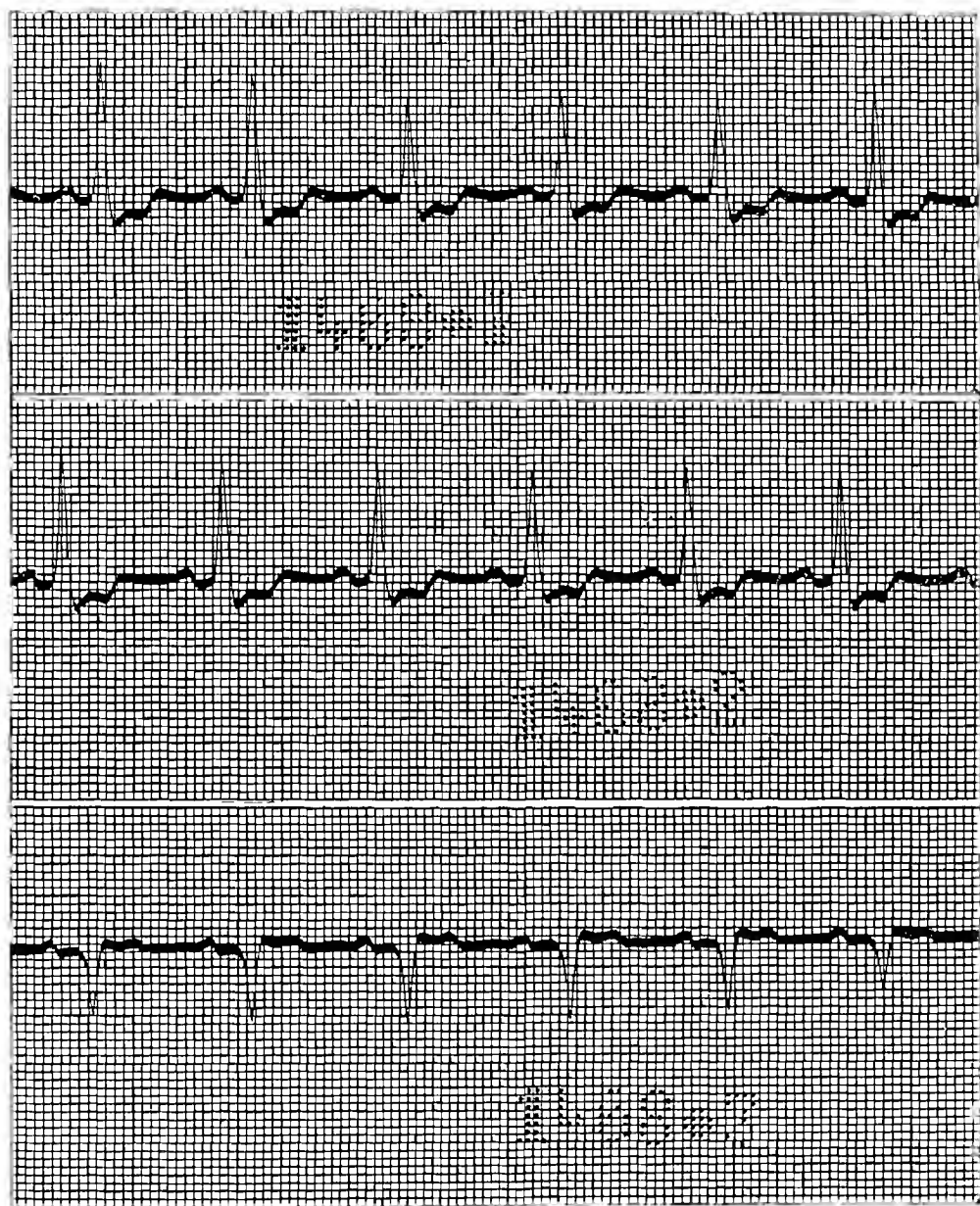


Fig 5—Electrocardiogram taken same day as the x-ray of the heart shown in figure 4, cardiac rate, 88, tracing characteristic of digitalization, left sided preponderance becoming more marked

cardiac rate of 160 beats a minute, and the electrocardiogram revealed tachycardia of nodal origin. He exhibited pulsus alternans during this period of decompensation, and developed a large right pleural effusion. During the period that the patient was taking ephedrine, his condition

grew worse, and he said that following each dose of the drug the tremor, sweating and discomfort increased

Following the discontinuance of ephedrine and the use of digitalis in adequate doses, accompanied by complete rest in bed, he showed steady improvement, the pleural effusion disappeared, and he returned to a comparatively normal state in a short time

The serious nature of the effects of this drug would seem to justify a report on this case in order that more caution be urged in guarding against such effects in the future

This case appears to bear out in all respects the observations of other observers regarding the danger of using ephedrine in treating patients who have damaged hearts. We believe that before ephedrine can be safely administered, the patient should be subjected to a careful examination of the cardiovascular system in order to determine whether disease of this system exists and whether or not the drug is contraindicated

This case also illustrates the not uncommon mistake of diagnosing so-called "cardiac asthma" as true bronchial asthma. Furthermore, it shows that even in patients who exhibit signs of true bronchial asthma, a careful examination of the heart is indicated. When evidence of cardiac damage exists, ephedrine should be used with extreme caution, if any evidence of toxic symptoms develops the drug should be discontinued promptly

We also feel that attention should be called to the fact that while this drug is highly extolled and widely exploited at present, the physician does not necessarily have to prescribe it and may make use of the other well known remedies for bronchial asthma. The following conclusions appear to be justified

- 1 Ephedrine is a dangerous drug to use when patients show evidence of cardiac damage

- 2 Extreme care is necessary in the diagnosis of bronchial asthma, as not infrequently cases of so-called "cardiac asthma" are put in this group

- 3 Ephedrine may produce acute cardiac decompensation and pulsus alternans in patients with damaged hearts

- 4 If during the administration of ephedrine the patient exhibits any toxic symptoms such as palpitation, tachycardia, arrhythmia or vasomotor disturbances, the drug should be promptly discontinued

- 5 Pulsus alternans does not have the serious significance for patients who exhibit this condition with tachycardia as it has for persons with a normal cardiac rate

- 6 The sale of ephedrine to the layman should be discouraged, and even its indiscriminate use by the physician is to be deplored

SEPTICEMIA DUE TO A STRAIN OF THE BACILLUS MUCOSUS-CAPSULATUS GROUP IN A CASE OF DIABETES MELLITUS*

EDWARD H MASON, M D

AND

WILLIAM W BEATTIE, M D

MONTREAL

The occurrence of septicemia from infection with *Bacillus mucosus-capsulatus* is not generally recognized on this continent. In France, especially among the physicians of Paris, cases have been reported at infrequent intervals. In his thesis in 1917, Colombe¹ collected sixty cases from the world's literature. Of these sixty, only twenty-five were diagnosed during life by a positive blood culture.

In 1924, Caussade, Joltrain and Surmont² collected fifteen new cases that had been reported since 1917, and added one of their own. Since then, additional cases have been reported by Creyx³ and by Lereboullet and Pierrot⁴.

The present report is that of a case of *Bacillus mucosus-capsulatus* septicemia which was proved during life by two blood cultures and which terminated in death. Autopsy was not obtained.

REPORT OF CASE

History—R C M, a man, aged 55, was admitted to the Royal Victoria Hospital on April 10, 1927, complaining of general malaise and soreness in the left hip joint. Seven weeks before admission, after he returned from an automobile ride, a slight chill had developed. This was followed by chilly sensations for the next few days. For about five weeks he had suffered irregularly from "indigestion" with belching of gas after meals. These symptoms were also associated with infrequent attacks of dull pain in the left hip joint, which radiated to the knee and calf muscles of the left leg, the pain disappearing with rest.

One week previous to admission, a general feeling of malaise developed, which continued until April 9, when a physician was consulted, who reported a temperature of 101 F. The next day the temperature was 104 F, and the general malaise and weakness were more marked.

* From the McGill University Clinic, Royal Victoria Hospital, and The Pathological Institute, McGill University, Montreal.

1 Colombe, J. Les septicémies pneumobacillaires, Paris These, 1917, no 29 de la bibliothèque de la Faculté de Médecine de Paris.

2 Caussade, G, Joltrain, E, and Surmont, J. Septicémie à pneumobacille de Friedländer, Bull et mém Soc méd d hôp de Paris 48 148 (Feb 8) 1924.

3 Creyx, M. Sur un cas de pneumobacillemie, Compt rend Soc de biol 94 596 (March 12) 1926.

4 Lereboullet, P, and Pierrot, M. Un nouveau cas de septicémie à pneumobacille de Friedländer terminée par la guérison, Bull et mém Soc méd d hôp de Paris 51 128 (Feb 10) 1927.

Diabetes mellitus had been present since May, 1912, the onset being associated with typical symptoms. Since September, 1921, freedom from glycosuria had been maintained through dietetic control. With the present infection, glycosuria became constant.

Examination—The patient was a rather overnourished man, who appeared anxious and ill. The temperature was 104.8 F, the pulse rate, 100 and respirations, 28. The throat was not inflamed, and the pupils were equal and active. There was no general glandular enlargement. The lungs were normal except for an occasional moist r  le at the bases. The pulse rate was regular, and the vessel wall was not palpable. The heart was normal and the blood pressure was systolic, 140, and diastolic, 65 mm of mercury. The abdomen was normal.

The urine was acid, of a good specific gravity, and contained albumin and sugar. There was no acetone. The microscopic examination showed hyaline casts and a few red blood cells. The blood count showed 4,800,000 red cells and 90 per cent hemoglobin. White cells counts ranged from 7,500 to 9,000 per centimeter on four occasions. The stool was negative, except for an acid reaction.

On admission, the blood urea was 0.32 Gm per liter and the plasma carbon dioxide (capacity) was 50 per cent by volume. On April 15, the former was 0.60 Gm per liter.

Roentgenograms of the pelvis and of both hip joints did not indicate the cause of the pain in the left hip joint.

Two Widal reactions of the blood were negative for *Bacillus typhosus* and *Bacillus paratyphoid* A and B. Two blood cultures (April 10 and 15) and one stool culture yielded large numbers of a gram-negative, nonmotile bacillus, which proved to be a member of the *Bacillus mucosus-capsulatus* group.

Subsequent Course—The infection ran a rapid course, as will be seen from figure 1, death taking place on the seventh day after admission. Hyperglycemia, which was little affected by insulin, persisted. There was no ketonuria. Each evening, commencing on April 12, there was a severe chill associated with a rise in temperature. During the last day of life there was moderate abdominal distention with diffuse moisture in both lungs, although definite areas of consolidation did not develop. Mental stupor and unconsciousness then appeared, persisting until death.

MORPHOLOGIC AND BIOCHEMICAL CHARACTERISTICS OF THE STRAIN OF *BACILLUS MUCOSUS-CAPSULATUS* (KLEBSIELLA)

Bacteriologic Report—The organism isolated on two separate occasions from the blood and once from the stool showed the following morphologic and biochemical characteristics.

It was a gram-negative, short, stout rod, nonmotile and capsulated. The capsules were easily demonstrated in cultures grown in beef infusion broth, beef infusion agar, and even in peptone water (fig 2). On beef infusion broth, a uniform turbidity was soon produced, with a viscid creamy white ring and some sediment, later the culture became viscid. On an agar slant, the growth was creamy white, moist, raised, glistening and viscid. Gelatin was not liquefied. Litmus milk was acidified, coagulated and the litmus was reduced. The following carbohydrates were fermented, with the production of acid and gas: dextrose, mannose,

galactose, levulose, arabinose, xylose, rhamnose, mannitol, dulcitol, sorbitol, glycerol, maltose, lactose, sucrose, raffinose, inositol and salicin. Inulin and dextrin were not fermented. In peptone water after forty-eight hours, no indol was detected, but on two occasions, after incubation for nine days, a faint trace of indol was detected by Ehrlich's test (parabenzaldehyde). In nitrate broth, the nitrate was reduced to nitrite. The Voges-Proskauer reaction was positive.

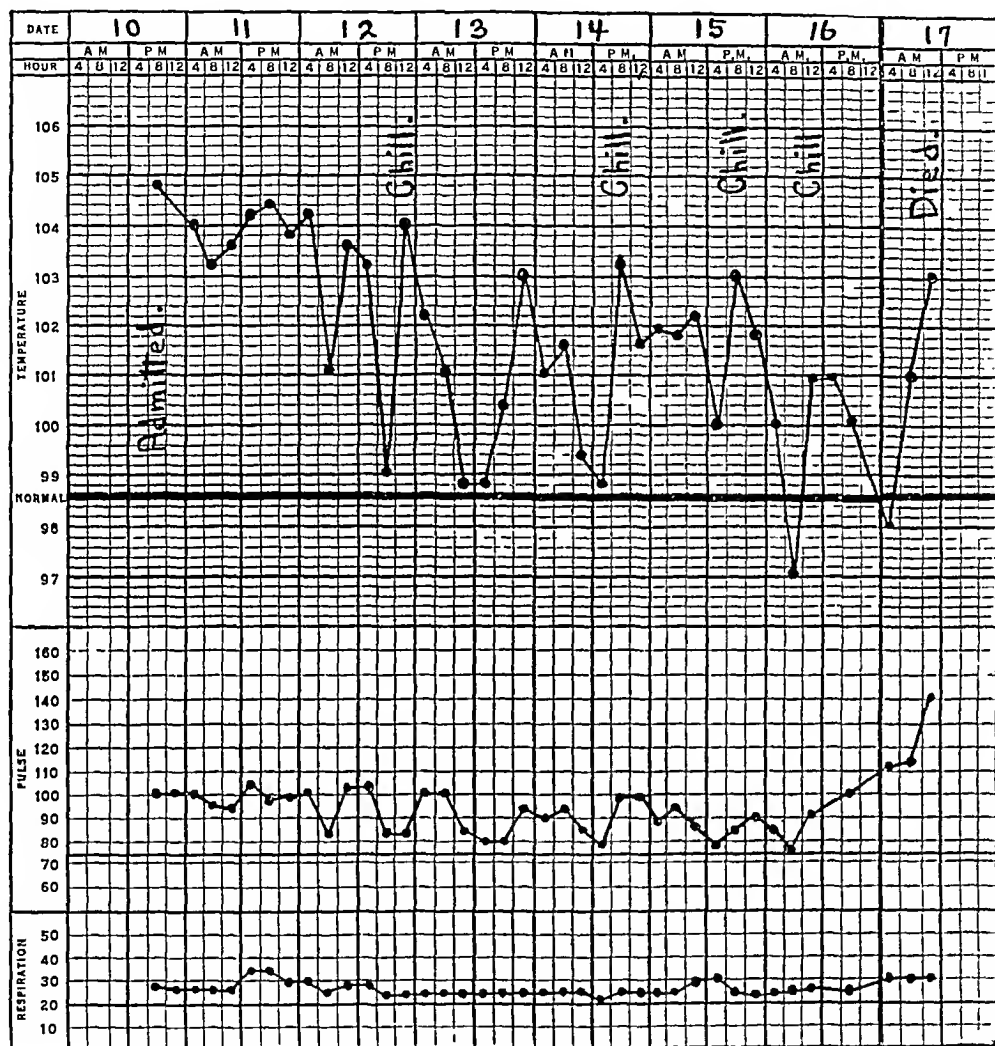


Fig 1—Chart showing the temperature, pulse rate and respiration throughout the course of the infection

PATHOGENICITY

As small a dose as 0.5 cc of a 1:100 dilution of a saline suspension of a twenty-hour growth on an agar slant, injected into the peritoneal cavity, killed a mouse in thirty-six hours. Larger amounts of the dilution killed five other mice more quickly.

Also an intraperitoneal injection of 0.25 cc of a twenty-hour broth culture killed two mice in five hours and two others within ten hours. Smaller amounts killed four mice within twenty-five hours. The peri-

toneal cavity contained a mucoid exudate, with polymorphonuclear leukocytes and gram-negative capsulated bacilli

Subcutaneous injection of 0.1 cc of a twenty-four-hour broth culture into the abdominal wall of a mouse was followed by a localized swelling, which was covered by a scab within five days and finally disappeared. Two tenths of a cubic centimeter of the culture injected in the same way into another mouse caused death on the fifth day. Autopsy revealed a phlegmonous swelling of the abdominal and thoracic walls, of the skin, subcutaneous tissue, muscle and peritoneum, and the peritoneal cavity contained a mucoid exudate the same as has been described. Histologic examination of the lesion in the abdominal wall showed dense infiltration of the subcutaneous tissue, muscle and peritoneum with an exudate of polymorphonuclear leukocytes, fibrin and serum, and enormous numbers of bacilli (fig. 3)

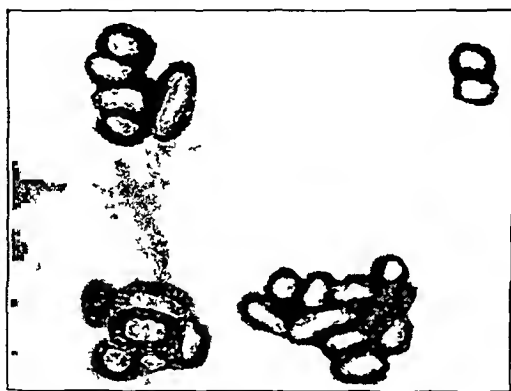


Fig. 2—Eighteen hour culture on plain nutrient agar stained with carbol fuchsin and nigrosin showing capsules

Five tenths cubic centimeter of the same twenty-four-hour broth culture was injected into the peritoneal cavity of a guinea-pig of about 300 Gm, and it was found dead in eighteen hours. The peritoneal cavity contained an exudate similar to that described, but no other gross lesions were noted.

The same twenty-four-hour broth culture (0.25 cc) was injected into the subcutaneous tissue of the abdominal wall of another guinea-pig, the animal remained lively and apparently well. An indurated swelling developed which subsequently ulcerated. On the ninth day, the ulcer was covered by a scab. Slight pressure caused a small drop of creamy white pus to exude. An organism identical with the original was isolated in pure culture from this pus. Eventually, the ulcer and induration were replaced by a small scar, complete recovery having taken place.

From all sixteen animals that died from inoculation, an organism identical (so far as tested) with the original was isolated from the heart's blood.

Of nine mice inoculated by instilling 0.1 cc of a twenty-hour broth culture into the nostrils, six died within seven days, and from five of these an organism identical with the original was isolated from the heart's blood.

In two of these animals, smears from the surface of the brain showed numerous gram-negative capsulated bacilli, morphologically identical with the original, also polymorphonuclear leukocytes. Paraffin sections of the brain of one of these showed that in the white matter there were numerous small abscesses containing leukocytes, and clear spaces filled, evidently, with serous material, and containing numerous gram-negative capsulated bacilli. Some of these abscess cavities communicated with the meninges, in which a similar exudate was found.

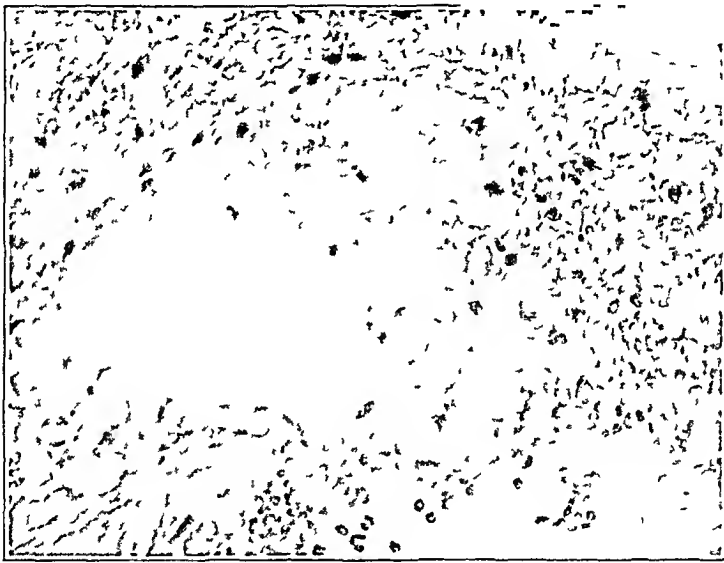


Fig. 3—Phlegmonous infiltrated thoracic wall of a mouse showing the organisms in enormous numbers.

In one of these two animals there was an abscess about 0.6 cm in diameter in the left side of the neck, filled with creamy white mucoid pus. Microscopic examination of this abscess showed a central mass of exudate, polymorphonuclear leukocytes, fibrin and serum with numerous gram-negative capsulated bacilli, surrounded by a wall of granulation tissue, which infiltrated the surrounding lymph nodes and lobules of the salivary glands. It appeared impossible to be sure whether the abscess primarily arose in a lymph node or in a salivary gland. An organism identical with the original was isolated from the abscess.

So far, attempts to infect guinea-pigs by instilling cultures into the nostrils have been unsuccessful.

A mouse, into the peritoneal cavity of which was injected 0.5 cc of saline suspension of the strain of organism isolated from the stool of

the patient, was found dead on the third day. The peritoneal cavity contained an exudate identical with that described in the other animals and, besides, three grayish-white nodules were found in the spleen, in the right kidney and in the liver. Paraffin sections of these nodules revealed abscesses similar to those already described, and showed the bacilli in enormous numbers. An organism identical with the original was isolated from the heart's blood of this mouse.

BACTERIOLOGIC CONCLUSIONS

The morphology, especially the capsule formation and mucoid growth, the biochemical reactions and its pathogenicity would place this organism in the *Bacillus mucosus-capsulatus* group (genus *Klebsiella*), except that it is "Voges-Proskauer" positive and that it ferments lactose. (However, the fermentation of lactose by organisms of this group is irregular.) The positive "Voges-Proskauer" reaction allies it to the *Bacillus aerogenes-cloacae* group (*Aerobacter*), and in sugar fermenting ability it corresponds to *Aerobacter oxytoca*, which differs from *Aerobacter aerogenes* in being dulcitol positive. It would seem best to consider it, at least temporarily, as a variant of the *Bacillus mucosus-capsulatus* group.

Three references to members of the *Bacillus mucosus-capsulatus* group giving a positive Voges-Proskauer reaction have been found in the literature.⁵ Investigation of this point in available strains is being undertaken.

CLINICAL CHARACTERISTICS OF THE INFECTION

On admission of the patient to the hospital, it was suspected that the infection was that of typhoid fever. Against this diagnosis was the rapid onset and the rise of the fever without the usual mental torpor and dulness. Rose spots did not develop, the spleen was not palpable, and there was no leukopenia. Subsequently, the Widal reaction as well as the blood culture for *Bacillus typhosus* was found to be negative, and the appearance of the daily chill was atypical.

This case followed the usual course as reported in many cases of *Bacillus mucosus-capsulatus* septicemia. As emphasized by Cleyx, there was no localization, the temperature was of the septic type, and no point of entrance was discovered.

⁵ Simonds, J. P. A Curious Accident due to Fermentation Caused by *B. Pneumoniae*, *J. Bact.* **2** 245 (May) 1917. Hewlett, R. Turner. A Manual of Bacteriology, Clinical and Applied, New York, The Macmillan Company, 1921, p. 413. Edwards, Philip R. The Relation of Encapsulated Bacilli Found in Metritis in Mares to Encapsulated Bacilli from Human Sources, *J. Bact.* **15** 245 1928.

In 1912, Brissand ⁶ when reporting fifteen cases of septicemia due to *Bacillus mucosus-capsulatus* stressed the gravity of the infection, the constancy of pulmonary manifestations and the tendency to hemorrhages. That the infection may not terminate fatally can be justly assumed from Lereboullet and Denoyelle's ⁷ report of two cases in children, aged 12 and 14, who recovered. In both instances, the diagnosis was proved by blood culture. Lereboullet and Picot ⁴ have also reported another proved case in a child of 13 years, in whom recovery took place.

In certain instances the infection has assumed pyemic characteristics resulting in abscesses of the kidney, liver and spleen, and not infrequently in gross-intestinal ulceration.

Urine and Blood Data

Date, 1927	Intake, Gm			Insulin Units					Urine			Blood		
	Pro- tein	Fat	Car- bohy- drate	A M N P M					Volume, Cc	Dex- trose, Gm	Ace- tone	Sugar Percentage		Carbon Dioxide Capacity, per Cent by Volume
												Before Eating	After Eating	
April 10	50	100	50						430	3.8	0	0.321		50
April 11	50	100	50						2,050	13.7	0	0.218	0.246	47
April 12	50	100	50	7			10		1,360	25.2	0		0.230	
April 13	23	54	36	5	5		10		940+	12.1	0			
April 14	34	77	39	10	5		15		1,400	16.8	0	0.327	0.318	49
April 15	50	125	100	15	10		15		1,530	11.5	0	0.339	0.330	
April 16			45	15	15		15		550+	3.1	0	0.315		
April 17			10	5					Lost					

THE DIABETIC STATE

That the infection caused an exacerbation of the diabetic condition is evident. No degree of acidosis developed, but the blood sugar showed little response to insulin therapy as is usual with infection. The persistent hyperglycemia probably worked deleteriously on the course of the septicemia. These data are shown in the table.

SUMMARY

1 A case of septicemia due to a member of the *Bacillus mucosus-capsulatus* group giving a positive Voges-Proskauer reaction is reported.

2 The portal of entry of the infecting organism was undetermined. The infection ran a rapid, septic course terminating fatally without localization.

3 The case was complicated by the presence of diabetes mellitus.

⁶ Brissand, H., Cordier, V., and Badolle, A. La pneumonie a pneumobacilles, Lyon méd **118** 817 1912.

⁷ Lereboullet, P., and Denoyelle, L. Deux cas de septicémies graves a pneumobacille de Friedlander terminées par la guérison, Bull et mem Soc med d hôp de Paris **48** 226 (Feb 29) 1924.

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS *

HENRY A CHRISTIAN, M D

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In 1921, I had the opportunity to study a patient with a pathologic condition to me entirely unique. At that time, I did not succeed in finding similar cases reported in the literature. I was at a loss to give a satisfactory name to the condition or disease, and so did not place it on file in the literature. Recently, in a report of a meeting of the Association of Physicians of Great Britain and Ireland, held May 29, 1925, I saw a brief notice of an entirely similar case, reported by F. Parkes Weber, and subsequently read his report in the *British Journal of Dermatology and Syphilis*.¹ The name he used intrigued me, now, with a title for my report, it seemed appropriate to present my observations before the Association of American Physicians, which furnished a model for the society before which Weber made his report.

The name used by me, febrile relapsing nodular nonsuppurative panniculitis, is descriptive of the process. I have added "febrile" to the terminology that Weber used to emphasize a feature which is striking and the one most likely to arouse the interest of the internist. There is fever in recurring attacks or relapses, there is inflammation of the pannicle, or panniculus adiposus, nodular in distribution and nonsuppurative, the panniculitis results in localized atrophy of the panniculus adiposus, subsequently causing a depression in the contour of the skin and giving a marked appearance of scarring. The patient is seriously sick. The cause of the inflammation remains unknown. In my study, blood cultures and cultures from the nodules were sterile. Organisms could not be found in excised tissue. In my patient, leukocytosis did not accompany the febrile periods. Histologically, in a healing lesion excised in 1920, I found in places edema and necrosis of the fat tissue, edema of the connective tissue between fat lobules, and a focal infiltration between the fat cells and in the connective tissue septums of lymphoid cells, plasma cells, young connective tissue cells, endothelial cells phagocytic for fat droplets, a few polymorphonuclear leukocytes and a rare foreign body giant cell, so that much of the subcutaneous adipose tissue thus was infiltrated. Fatty acid crystals were not present. Blood vessels, as a rule, were normal. A few showed periarteritis, rarely one showed endarteritis with proliferation of the endothelial cells.

* Reported at a meeting of the Association of American Physicians, Washington, D. C., May 3, 1928.

1 Weber, F. Parkes. *Brit J Dermat* 37 301, 1925.

The inflammatory process did not extend to the dermis, and so the skin itself was not scarred. No organisms were seen. The process is well shown in the accompanying photomicrographs (figs 1 to 7), which will serve in place of a more detailed verbal description.



Fig 1—Low power magnification of area of panniculus adiposus in a case of "relapsing febrile nodular nonsuppurative panniculitis"

REPORT OF A CASE

History—A single woman, aged 25, was admitted to the Peter Bent Brigham Hospital on Feb 5, 1921, for observation. She was of native American stock, intelligent, a college graduate and a chemist. She had never been in the tropics. The family history was negative. She had had mumps and whooping cough in

childhood, and scarlet fever at the age of 12, followed by otitis media. Her disease first appeared in 1918 with a lump under the skin of the right upper arm, followed in six months by a similar lump over the left scapula. In 1919, many lumps, described as of pea to lemon size, appeared over both lower legs. They developed in a short time. At first they were reddened, and the patient believed they were associated with some diffuse swelling from the middle of the tibia to the

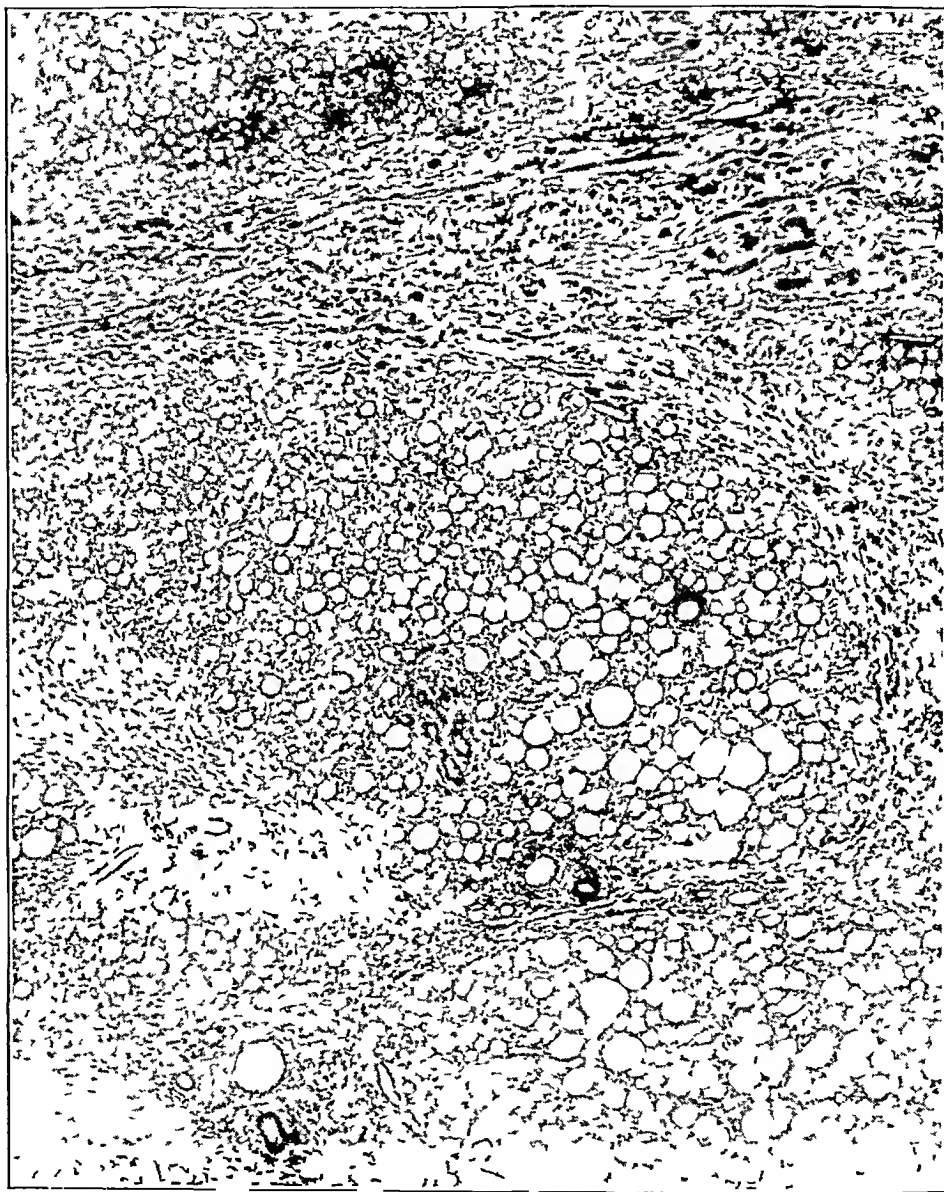


Fig 2—Low power magnification of area of panniculus adiposus showing marked inflammatory infiltration

ankle. A month after the appearance of the nodules on the legs, she began to have fever associated with headache, nausea, vomiting and muscle pain. The fever fluctuated daily, but the time of highest temperature was not constant each day. For a time these variations of temperature reached a daily higher level, and then lessened each day until the normal again was reached. Defer-

vescence lasted longer than the rise. During the course of fever, other lumps might appear. The lumps would gradually flatten out, seem to attach themselves to the skin and finally leave a depression. After the temperature returned to normal, the patient felt well for four months. Then in the course of two to three weeks at least fifty new lumps appeared, with fever, chilly sensations, nausea and vomiting lasting about one month. In this attack only the

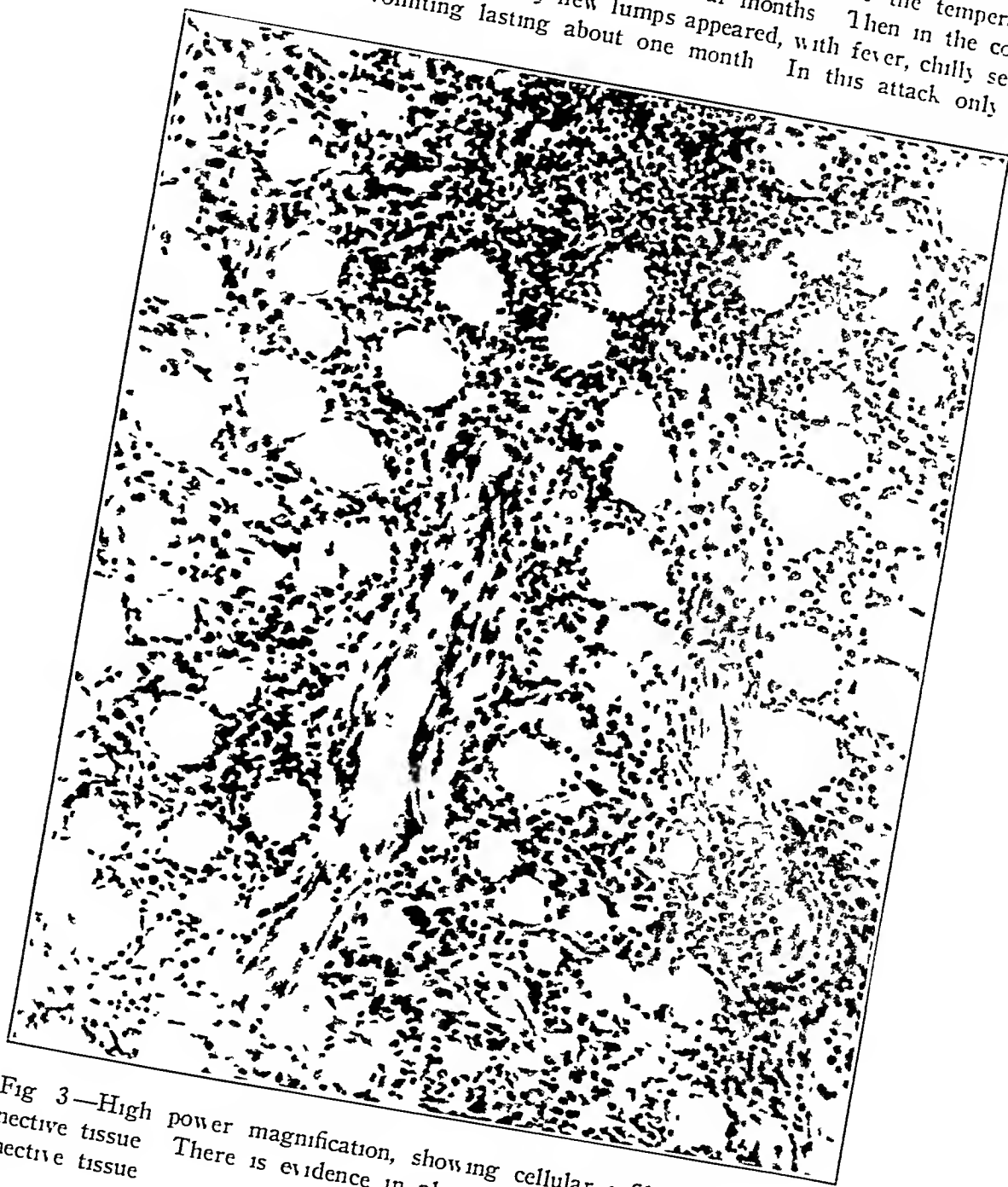


Fig 3—High power magnification, showing cellular infiltration of fat and replacement of fat by young connective tissue. There is evidence in places of replacement of fat by young connective tissue.

face, right forearm, palms of the hands and soles of the feet were spared. There was an interval of one month, then the third attack began and lasted for five weeks. A fourth attack occurred nine months later, in June, 1920, and lasted for a month (fig 9 shows the fever curve in the latter part of this attack). After an interval of two months, a fifth attack developed. This was the most severe one

to date (fig 10 shows the fever curve) and, in addition to previous symptoms, was accompanied by a slight dry cough with a "catch" over the lower sternum and slight jaundice for one day. Fever persisted for over five weeks. Between the fourth and fifth attacks the patient felt continuously tired. The sixth attack began on Jan 24, 1921 with chills, fever and a dry cough. In this attack, she entered the Peter Bent Brigham Hospital on Feb 5, 1921.

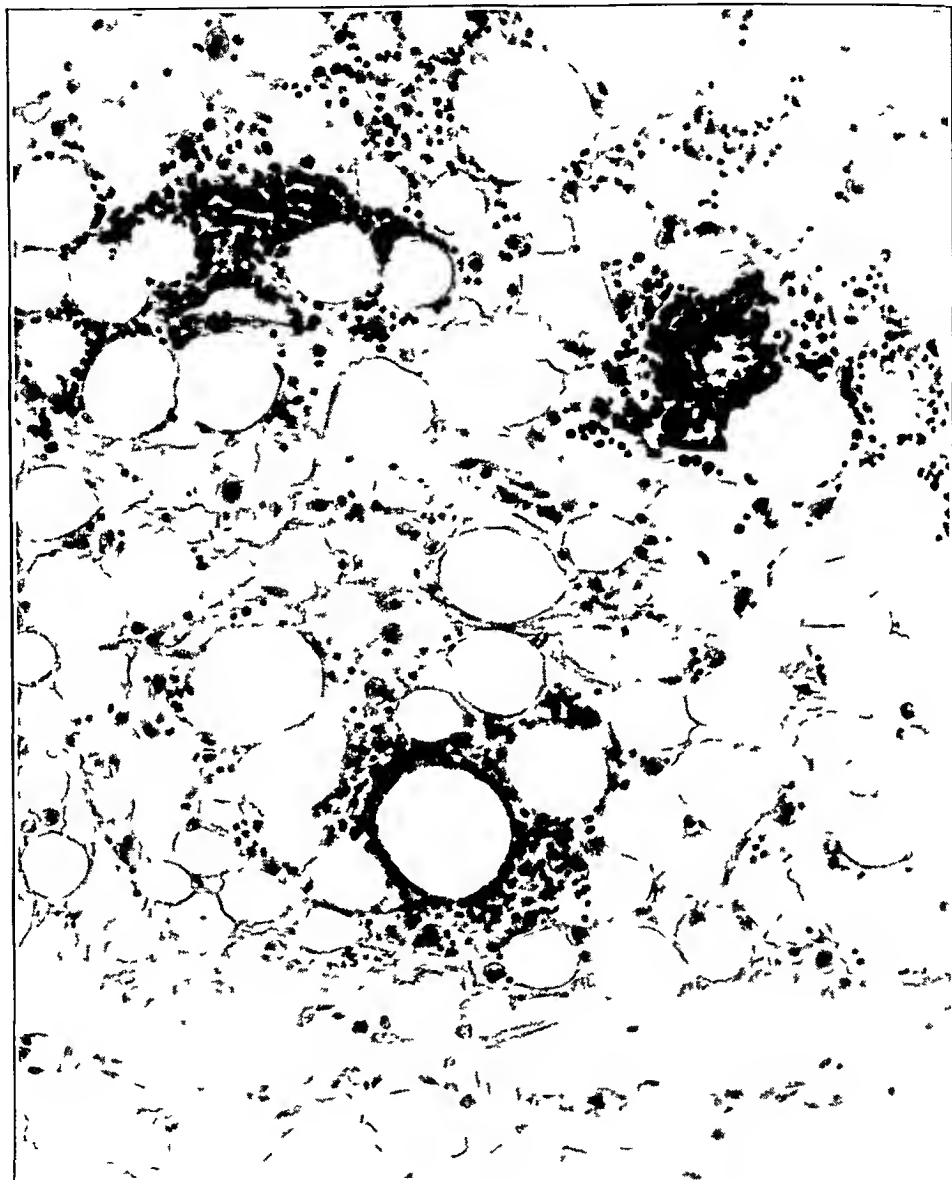


Fig 4—High power magnification, showing cellular infiltration of fatty tissue and a few macrophages

Examination—With the exception of the observations made on the subcutaneous tissue, the results of the physical examination were negative. Laboratory examination revealed urine normal, hemoglobin, 85 per cent, red blood cells, 4,929,000, white blood cells, 3,000. The differential count showed polymorphonuclears, 55 per cent, lymphocytes, 45 per cent. Five days later, there were 4,200 white cells, 50 per cent polymorphonuclears, 47.5 per cent lymphocytes

and 25 per cent large mononuclears. Six days later, the white cell count was 6,100. The Wassermann reaction was negative. The blood culture on Feb 6, 1921, did not show any growth (on June 15, 1920, and on Nov 11, 1923, blood cultures did not show growth). The basal metabolic rate was -12 per cent. Figure 11 shows the fever curve of this, the sixth, attack. Cultures made from the nodules on Nov 11, 1923, were negative.

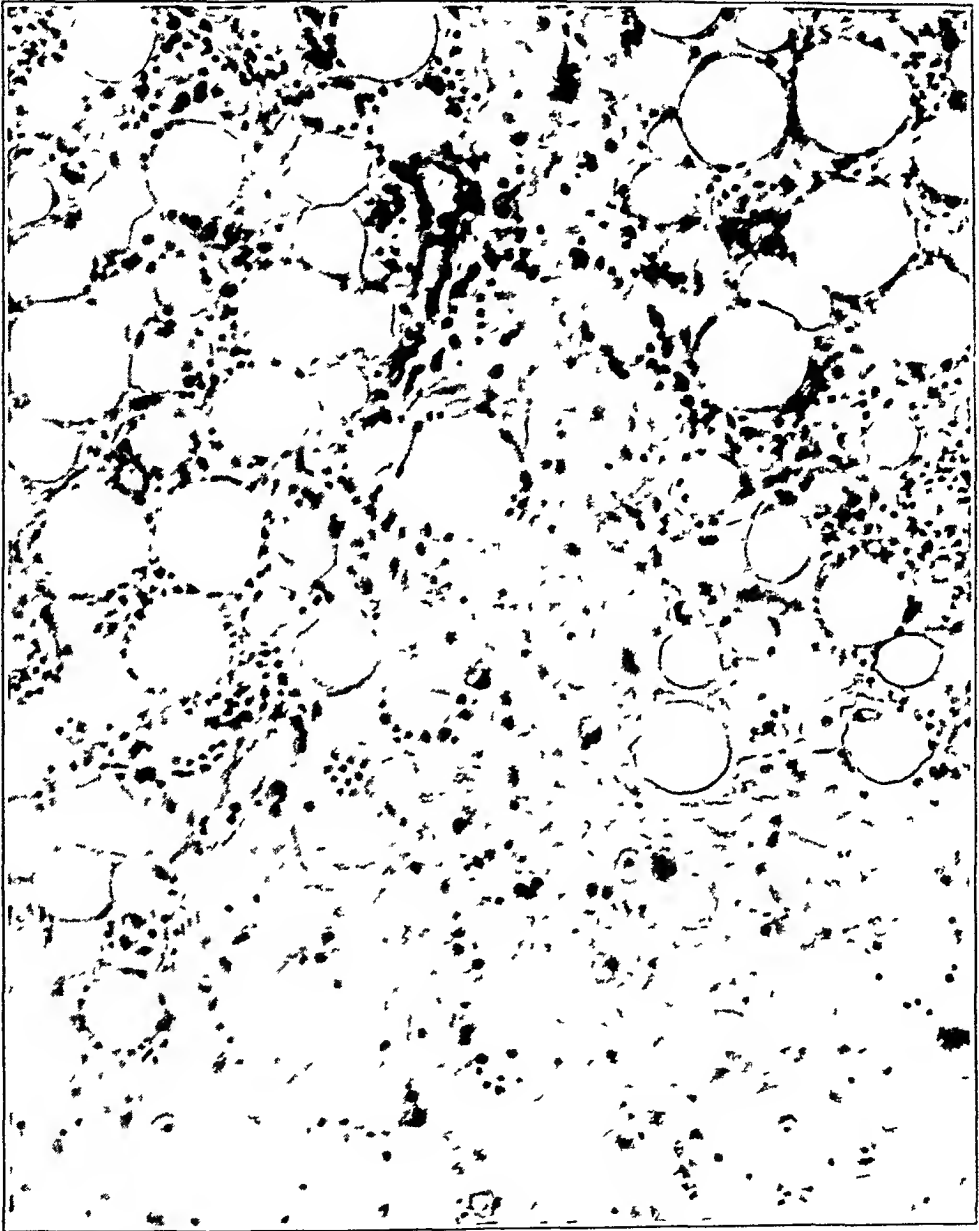


Fig 5—High power magnification, showing more macrophages and an area of edematous connective tissue

Clinical Observations—The skin condition (sixth attack) was described at the time by me as follows: "The striking thing, seen at first glance, are deep, irregular depressions in the cutaneous surfaces, distributed as will be described, not symmetrical in distribution and usually without color change in the skin (fig 8). There is no local heat. The left lower leg shows, as the most striking phenomenon, an unsymmetrical contour due to irregular depressions with intervening slight

elevations, more marked between the middle of the tibia and the knee than below, and rather more marked on the external than on the internal surface. Over the region covered by the anterior surface of the tibia, just above the mid-point, there is a definite swelling with ill defined margins, measuring 5 by 7 cm, the middle slightly reddened, being a dull, pale red, that almost disappears under pressure, leaving a slightly pale brownish background. This area does not pit on pressure.

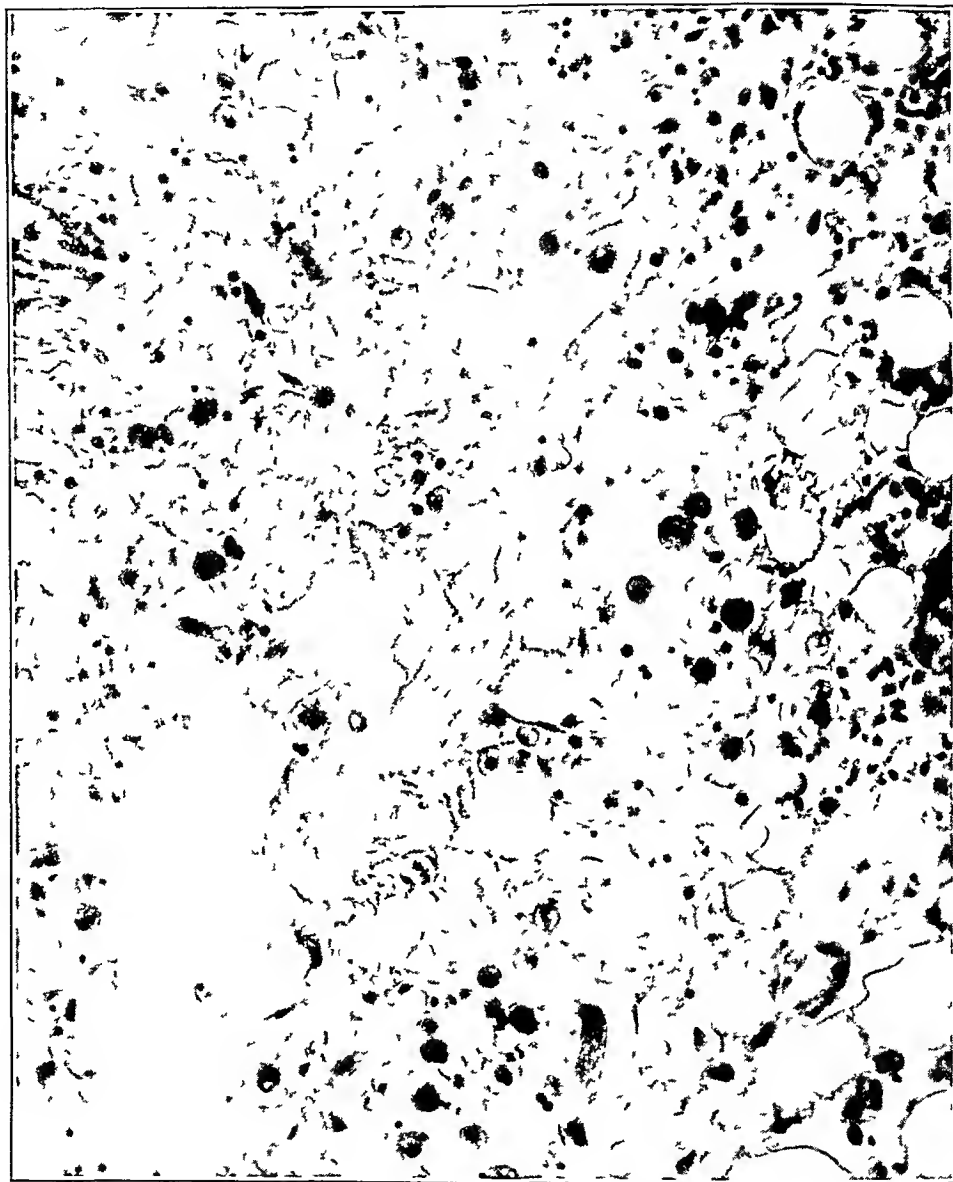


Fig 6—Similar to figure 5, with small area of necrotic fatty tissue at one margin

On palpation this nodule of swelling is not of uniform consistency, but has slightly firmer portions with intervening softer portions, giving a vague sense of fluctuation. At the outer surface of this is a depression about 3 cm in length by 2 cm in width with indistinct margins, apparently the result of a loss of subcutaneous tissue. Just above the outer side of this depression is another slightly elevated

area about 2 cm in diameter, rather firmer than the elevation first described. Like the first one, this is vaguely outlined, apparently shading off into surrounding normal tissue. Over these elevations the skin can not be picked up in folds as well as over the unaffected part, and much less well than over the depressed areas. The texture of the skin over all of these places seems normal, and there is no

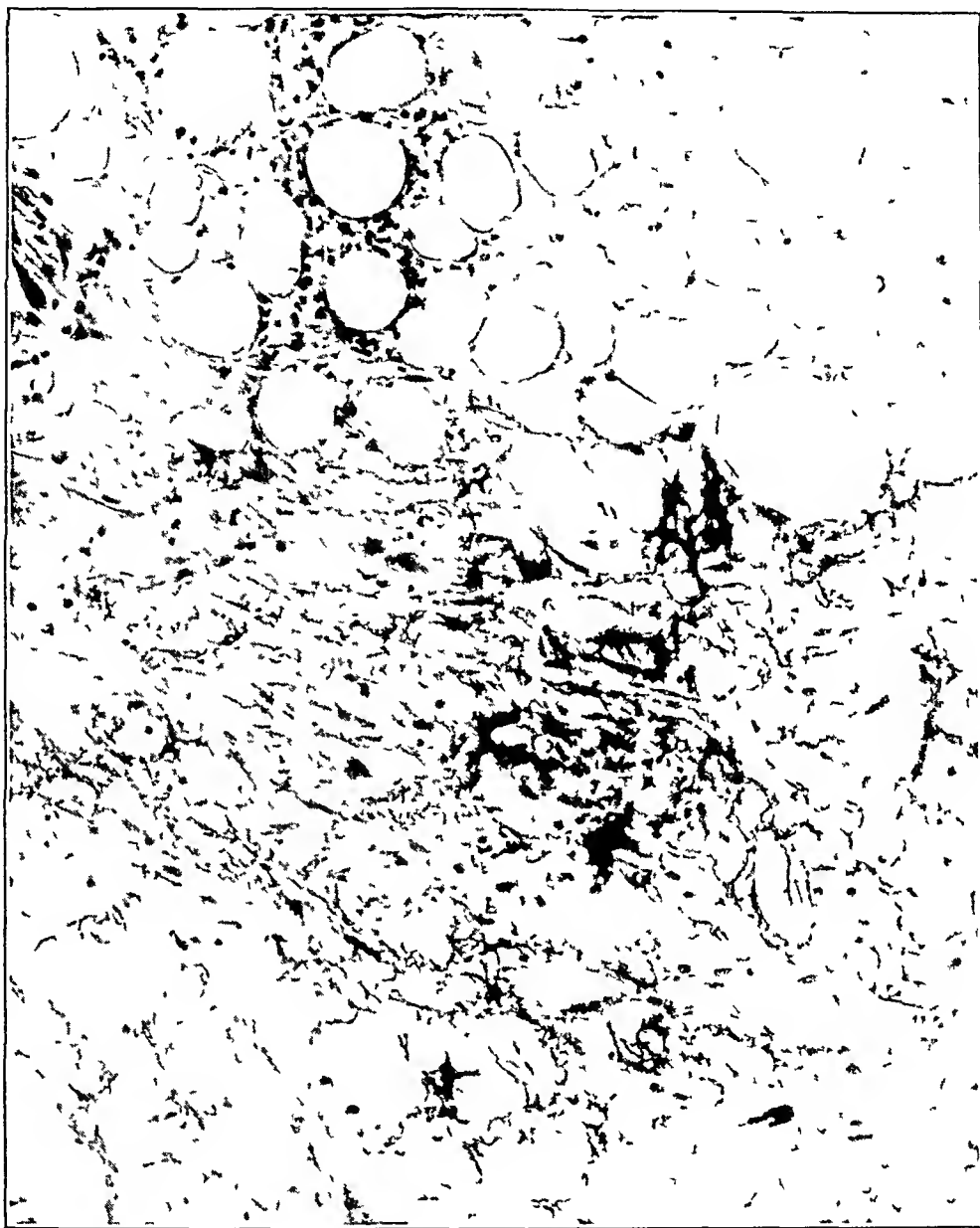


Fig 7—High power magnification, showing necrotic fatty tissue and an area with fibrin threads

firm induration to be made out of either the swellings or the elevations. Over the lower half and outer surface of the leg, there seems to be considerable diffuse atrophy of the subcutaneous tissue, which leaves the surface depressed, the skin feels a trifle thickened, but may be picked up easily in folds. The skin here has a slightly brownish discoloration. This is one of the older lesions and represented at one time a diffuse uniform swelling.

"Just between these two areas, but more posteriorly on the leg, is the only lesion that has developed during this period of fever. It appeared on February 12, noticed at that time by the patient as a slight local discomfort, feeling somewhat tender and like a little nodule under the skin. This was very indistinct, and I was uncertain as to whether at this time I could make it out definitely. Two days later, there was a definite, though not very firm nodule at this point, apparently in the subcutaneous tissue, not more than 0.5 cm in diameter. It subsequently has not increased in size. About the middle of the calf of this leg, there is a depression. Along the inner surface of the leg, there are irregularities of subcutaneous tissue, not visible swellings but areas which are felt as distinct irregularities, more



Fig 8—Deep irregular depressions in the cutaneous surface of the legs of a patient suffering from an attack of relapsing febrile nodular nonsuppurative panniculitis

flattened than those already described, and feeling a bit as if the skin were attached slightly to them. To one's fingers, moving up and down the leg, they give the sensation of irregular, beaded or button-like masses not entirely separated from each other and extending in a linear arrangement. There are none of these on the dorsum or sole of the foot.

"The right leg shows a similar irregularity of contour, with depressions from 3 to 5 cm in diameter, and intervening moderately elevated areas, as described for the other leg. Just as on the left leg, so on the posterior surface of the right leg there is a band or string of irregular nodules extending from a little below the

knee nearly to the ankle. None of these areas looks as red as those on the left leg, but the skin in places shows a slight redness and quite definite brownish discoloration. None of these masses seems attached to the deep fascia over the muscles, and they apparently are not attached to the muscles or tendons.

"On the upper right leg there are larger, similar depressions with intervening indefinite elevations. Just over the thigh region, a little anterior to the head of the femur, there are rather deep depressions. In between these are no definite nodules, but the subcutaneous tissue in places feels firmer than normal. The upper leg on the other side shows much the same picture.

"The right hand and forearm do not show any lesions. The left arm shows a depression on the forearm on the outer surface a little below the elbow. The upper right arm shows a scar slightly above the elbow where a nodule had been excised for examination, and just back of the deltoid muscle there is a very definite depression. Over the insertion of the deltoid there are vague swellings, but nowhere on the upper arm are these swellings definite or firm. The upper left arm is quite similar in general to the right. Just beneath the outer border of the left clavicle there is a deep depression, in which the subcutaneous tissue has entirely disappeared. Here the skin is not indurated, and no irregularity or thickening is felt. There have been no lesions on the neck, face or scalp. There are a scar and a depression from one of the early lesions over the middle of the left scapula. In the lower right axillary region there is a moderate depression. In the lumbar region, just over the lower right half, there is a depression 3 to 4 cm. in diameter, and at its lower border is a small, irregular nodule in the skin. On the abdomen are scattered irregular, smaller depressions with, in places, irregularities to be felt in the deeper subcutaneous tissue."

For two years the patient remained well, but in February, 1923, a seventh attack began with typical lumps developing on her legs. She kept at her work as a chemist until May 10, 1923, though during the latter part of the period she had a daily afternoon temperature of 100 F. On that date, her temperature rose to 103 F, and many new lumps appeared, chiefly on the legs, but also on the arms and back, nausea developed and she felt worn out. By June 1, this attack was over. On August 3, an eighth attack began, with many lumps and a rise of temperature to 102 F. This attack lasted two months, but thereafter the patient continued to feel bad and to ache as if she were going to have grip, her ankles felt tense, and at night were slightly swollen. I saw her again on November 7. The lesions on the skin were much as previously described, they felt firm and seemed to be in the subcutaneous tissue, they were not tender, the depressed areas were rather darkly pigmented. The ankles were red and tender, and the right felt brawny to the touch. The results of the general physical examination were negative. The blood showed hemoglobin, 96 per cent, white cells, 3,800, and red cells, 4,992,000. The urine was normal. The patient gradually improved and was well until about the middle of July, 1924, then a ninth attack began, of the usual character and length.

After recovering from the ninth attack, the patient remained well until the latter part of November, 1927, then a tenth attack began. The character of this attack was much like that of the others and it lasted into January, 1928. Late in February, 1928, when well along in convalescence from her tenth attack, the patient developed acute appendicitis, she was operated on, and complications did not follow.

Weber's case, also that of a woman, aged 50, was observed in three attacks accompanied by fever. His description and the photomicrographs

in his report show that the conditions he observed were very similar to those observed in my case, except that the bit of tissue from his patient showed more multinuclear giant cells than that from mine. I find no other essential difference between his case and mine. Weber seems to have considered his case as possibly unique, though he believed that it should be regarded as allied to Whitfield's ² type of erythema induratum.

In 1916, Gilchrist and Ketron,³ under the title, "A Unique Case of Atrophy of the Fatty Layer of the Skin Preceded by the Ingestion of the Fat by Large Phagocytic Cells, Macrophages," described a girl aged 8 in Baltimore whose mother stated, in giving the child's history, that "she had had feverish attacks and loss of appetite on several occasions," and who showed changes in the legs (illustrated in the article by' photographs) strikingly similar to those observed in Weber's patient and in mine. The 8 year old patient had slight fever while in the hospital. The changes were confined to the legs. Excised bits showed, on microscopic examination, appearances similar to those described by Weber and by me, changes confined to the subcutaneous fat. Looking at the illustrations and reading the descriptions of Gilchrist and Ketron, one can but feel that the condition is the same as that described by Weber and me. Weber used, too, in his title the words, "showing phagocytosis of fat cells by macrophages."

Warfield ⁴ has made a report of a condition under the descriptive title of "Multiple Symmetrical Gangrene of the Fat of the Abdominal Wall in a Case of Alcoholic Neuritis," which may be closely related to the disease here being described. Unfortunately, excised tissue was lost before histologic examination could be made. In Warfield's case, the subcutaneous tissue became gangrenous and the skin ulcerated, it did not in the three cases just reviewed, but there was the feature of indurated lesions in the panniculus, developing in succession.

In 1922, Lee and Adair ⁵ described a condition, unique in their opinion, under the title "Traumatic Fat Necrosis of the Breast," in which the tissue has some similarity in histology to the tissue from the cases under discussion here. They believed that in their patients trauma had been a causative factor, leading to necrosis of the fat tissue of the breast with subsequent cellular infiltration. Perhaps this condition bears some relation to the more generalized distribution of focal areas of inflammation of the subcutaneous fat described here.

2 Whitfield. *Am J M Sc* **122** 828, 1901

3 Gilchrist and Ketron. *Bull Johns Hopkins Hosp* **27** 291, 1916

4 Warfield. *Ann Clin Med* **5** 884, 1927

5 Lee and Adair. *Surg Gynec Obst* **34** 521, 1922

The term panniculitis is used, too, in a somewhat different relationship, expressive of a form of chronic rheumatic disease. Stockman,⁶ for example, has just published a paper under the title "Chronic Muscular Rheumatism and Panniculitis," in which he says:

Panniculitis is a fibrositis of the panniculus adiposus, and has the same etiology and pathology as fibrositis generally. Its anatomical distribution, however, confers on it certain clinical characteristics which merit some special description. The new fibrotic tissue assumes two forms, according to its situation. Over the deltoids, shoulders, back, flank, upper abdomen, hips, and outer sides of the thighs it is dense and evenly spread, giving the skin a hard brawny feel, while on the inner surfaces of the upper arms and thighs, abdomen, and pectoral regions it is in numerous pea-like masses lying in the subcutaneous fat and often forming veritable fibro-fatty pads at the inner sides of the knees and elsewhere. The little masses can be easily felt, and are exceedingly tender on pressure, as is likewise the whole subcutaneous overgrowth. Sometimes distinct encapsulated

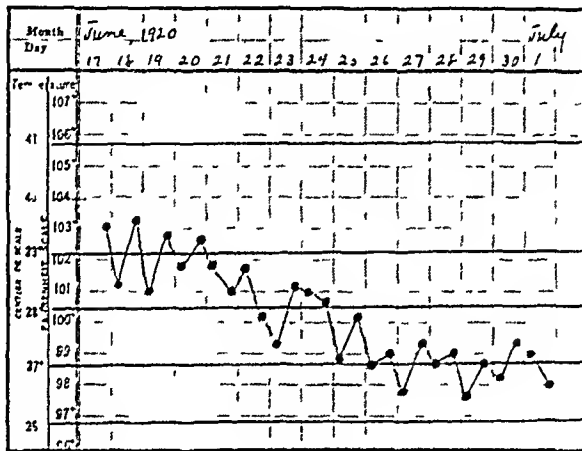


Fig 9—Temperature curve of the patient during the fourth attack of relapsing febrile nodular nonsuppurative panniculitis

lipomata are found, and these have a core of inflamed fibrous tissue, as if the local irritation had determined their growth.

He regards this as an extremely common condition. The nodular form, as described by him, has some resemblance to the condition described in the present paper and conceivably might be a mild form of it. The exact relationship of Stockman's panniculitis to acute rheumatic fever is not very clear from his paper, though he seems to think that there is some relationship.

There is another condition that may be closely related to relapsing febrile nodular nonsuppurative panniculitis, which I have seen through the courtesy of colleagues at the New England Children's Hospital.⁷

6 Stockman. Brit M J 1 293, 1928

7 Wilens, Gustav, and Derby, Joseph. Calcification of Subcutaneous Tissue in a Child (Calcosus Universalis), Am J Dis Child 31 34 (Jan) 1926

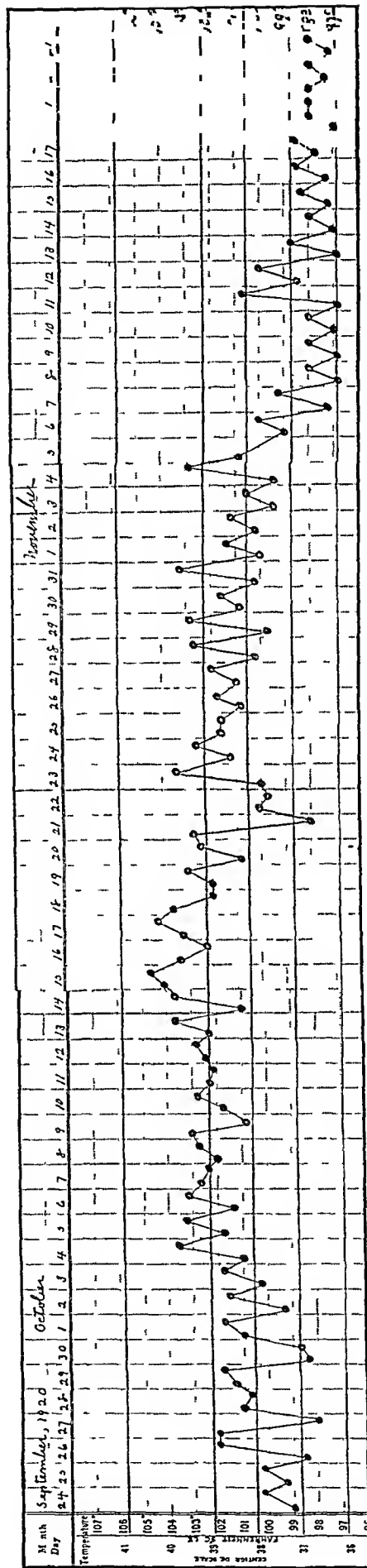


Fig 10 —Temperature curve during the fifth attack

In this condition areas of calcification occur in the subcutaneous fat, presumably following inflammation and necrosis. It is a question whether cases of this kind should be included. In certain respects, they seem unlike enough to be regarded, for the present at least, as of a different clinical entity. In some of the reported cases, in addition to calcification, there are changes in the tissue suggestive of those described in this paper.

The fever and relapses suggest that the condition here being reported may be a manifestation of undulant fever (infection with organisms of the *mellitensis abortus* group). But cultures in my case were negative, and there was no opportunity at the time of observation to test the serum for immunity reactions to fit such a hypothesis.

Possibly a more diligent search of the literature would reveal the fact that other patients have suffered from the disease represented by

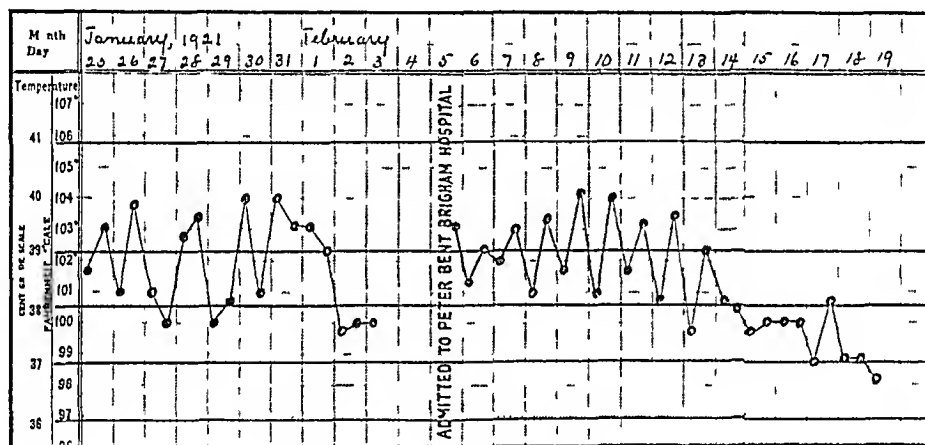


Fig 11—Temperature curve during the sixth attack

the three cases of Gilchrist and Ketron, Weber, and myself. It seems to be a reasonably definite clinical entity, possibly a syndrome, rather than a disease. The severity of symptoms with fever during attacks and their repetition again and again are most notable.

SUMMARY

There is a disease characterized by recurring attacks of fever, associated with a peculiar nodular inflammation of the subcutaneous tissue. Some of the fatty tissue necroses, and much of it becomes infiltrated with lymphoid and plasma cells. Macrophages take up fat in fine droplets. A few foreign body giant cells form. There results in time atrophy of the inflammatory nodule causing a depression in the contour of the skin. Suppuration does not occur, and the continuity of the skin is unbroken. The cause of the disease is unknown. The term "relapsing febrile nodular nonsuppurative panniculitis" is descriptive of the condition.

PANCREATOGENOUS FATTY DIARRHEA

REPORT OF A CASE *

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A case of pancreatogenous fatty diarrhea caused by chronic pancreatitis with extensive formation of calculi in the secretory ducts is discussed in this article. In a previous paper¹ I discussed this condition in detail, I shall now review some problems concerning the pathogenesis of the condition which were not discussed in that paper

REPORT OF CASE

History—A stevedore, aged 43, was admitted to the hospital on Dec 17, 1926, and was discharged on March 13, 1927. It was said that he had been born with "scaly skin," ichthyosis, his brother and his uncle were said to have suffered from the same condition. The skin lesions, however, had improved considerably during recent years. Twenty-five years previous to admission he had been a sailor, and had visited a number of ports during a period of one and a half years, but had never been south of Algiers.

For the past twenty years, he had worked as a stevedore. Six years prior to his admission to the hospital, he had had an attack of acute bronchitis, which was followed by frequent relapses. He was admitted to the Bispebjerg Hospital in December, 1926, for an acute attack of this condition. At that time, he did not pay any attention to his main ailment, the diarrhea. The patient drank as much as ten bottles of beer a day. He said that he had not had syphilis, the Wassermann reaction was —. In his youth, he had had gonorrhea.

During the past five years, the patient had suffered from diarrhea, from four to five pasty, semifluid but voluminous stools were passed in twenty-four hours. The diarrhea had varied somewhat in intensity, but it had been present throughout these years. He had soon noticed that the stools were lighter than normal, being straw-colored or yellowish gray. On standing, the stool was soon covered with a greasy layer of yellow oil, which seemed to exude from the excretion, this oil hardened rapidly, and then looked a great deal like butter. Sometimes this oily mass would pass from the rectum together with the stool, and in rare instances it would pass at night also. The patient noticed that the oil was most abundant when he was on a fatty diet. Occasionally he had had some slight oppression and nausea, but complained only of a gaseous dilatation of the abdomen. He had never suffered from pain, and he could eat any kind of food without discomfort. His appetite had increased markedly with the progress of the condition. He had lost only 11 pounds (5 Kg), in spite of an apparently large loss of fat through many years. Recently, however, he had become a little tired from working. Neither stomatitis nor icterus had ever been present.

Physical Examination—The patient looked healthy, perhaps slightly anemic, and was fairly well nourished. The tongue was somewhat coated, and showed

* From the Medical Department of St Elizabeth's Hospital, Copenhagen

† Delivered before Dansk Selskab for intern medicin

1 Thaysen, T E Hess. Acta med Scandinav 64 292, 1926

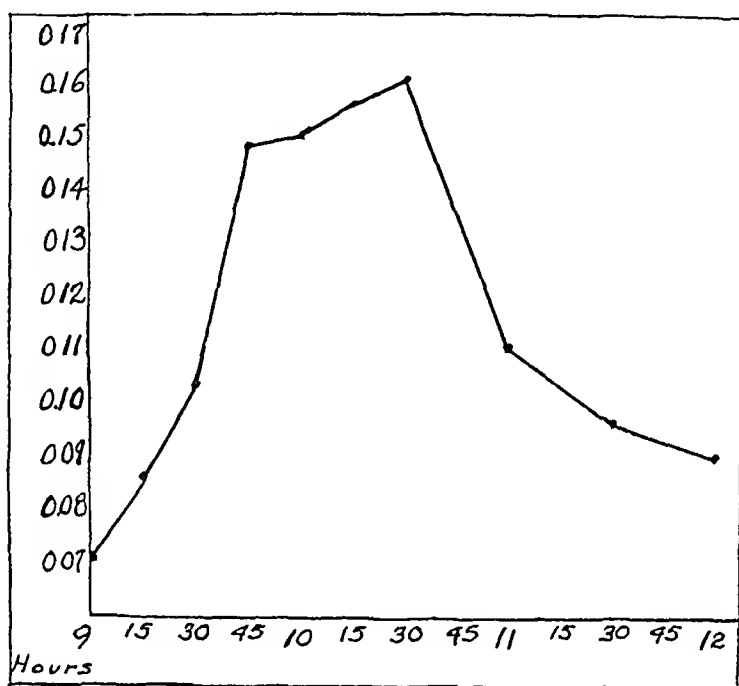
impressions of the teeth Neither stomatitis nor glossitis was present The organs of the neck were normal Icterus was not present The heart and lungs did not present any abnormality with the exception of a few rhonchi posteriorly

The abdomen was rather large, distended, puffy and inflated, but no tumor was found in the region of the pancreas Neither the liver nor the spleen was enlarged Ascites was not present

The skin was rather dry, with remnants of the condition of ichthyosis already mentioned The patient perspired readily He had an occipital alopecia areata

Numerous urinalyses revealed no albumin and sugar The basal metabolism was from 98.1 to 100.6 per cent (Du Bois-Benedict)

The stomach secretion was shown by the Ewald test meal to be 80+ 25 cc, Congo, 58/75, phenolphthalein, well chymified There was no retention after six hours



Blood sugar curve after ingestion of 50 Gm of dextrose

An examination of the blood (in Bispebjerg Hospital before admission) revealed hemoglobin, 73 per cent, red corpuscles, 3,650,000, white corpuscles, 6,800, index, 1, platelets, 298,000, and plasma color, 5 A later examination (Feb 23, 1927) showed the following hemoglobin, 72 per cent, red corpuscles, 4,400,000, white corpuscles, 5,000, index, 0.9 The differential blood count was normal

Three examinations of the blood sugar curve after ingestion of from 50 to 100 Gm of dextrose gave identical results The curve rose to about 0.163 and fell slowly, it did not return to the starting point in three hours (chart) Sugar was not present in the urine throughout the experiment

The stools were voluminous, as much as 1150 Gm were passed in twenty-four hours, they were yellowish white or grayish yellow, sour and foul-smelling On standing, they yielded a large, yellowish, butter-like mass which on examination proved to contain 87.74 per cent neutral fats, 9.77 per cent free fatty acids, and 0.24 per cent soaps (calculated as oleic acid)

Microscopic examination of the stool showed numerous droplets of fat, besides neutral fat (nile blue sulphate stain), many striated muscle fibers without nuclei, much starch, and granulose-containing bacteria, fermentation to 35 cc in Kemp's fermentation apparatus (normally about 10 cc)

The reaction to Schmidt's nuclear test was negative

On Feb 19, 1927, 1 cc of duodenal juice was tested every 10 minutes The results are shown in table 1

TABLE 1—Results of Duodenal Test

	pH	Lipase*	Trypsin†	Diastase‡
Jan 10, 1927		0	16.2	20.48
Feb 19, 1927	3.44	2.4	0	0
	3.35	2.0		
	5.56	1.6		
	6.35	1.6		
	7.31	1.3		
	7.22	1.2		
	7.7	1.1	0	32

* Determined by Bondi's method

† Determined by Gross' method

‡ Determined by Wohlgemuth's method

TABLE 2—Comparative Results of Analysis of Stools of Three Patients

N ^o		Age (Years)	Feces in 24 Hours, Gm		Elimination of Drystuff in 24 Hours, Gm		Fat Excreted in 24 Hours, Gm		Fat Ingested in 24 Hours, Gm		Loss of Fat in per Cent		Nitrogen Excreted in 24 Hours, Gm		Nitrogen Ingested in 24 Hours, Gm		Loss of Nitrogen in per Cent		Free Fatty Acids in per Cent of Excreted Fats		Free Fatty Acids Excreted, Gm		Soaps in per Cent of Excreted Fats		Soaps Excreted, Gm		Neutral Fat in per Cent of Excreted Fats		Neutral Fat Excreted, Gm	
M *	57	♂	256	27.9	9.89	250	3.96	1.6	13.9	11.5	12.4	1.25	57.5	5.68	30	2.97														
V K†	41	♂	734	174.6	85.3	136	62.7	9.71	19.8	53.9	36.3	48.8	5.4	6.0	37.5	31.8														
			734	186.9	101.12	136	74.3	9.63	19.8	48.5	57.2	36.7	5.9	4.6	57.8	58.8														
V T#	46	♂	1,030	262.7	132.5	95	139.5	16.8	17.6	97	65.2	87.4	5.7	7.5	29.1	38.56														
			147	51	21.3	72	29.4	3.2	16	21	75.9	16.2	10.4	2.2	13.7	2.90														

* M is the patient in an unpublished report of a case of pancreatogenous fatty diarrhea in mild diabetes, on examination the digestion of fat and protein was found to be normal

† V K is the patient discussed in this paper

‡ V T is the architect, mentioned in this paper, whose pancreas on autopsy was found to be atrophic

Roentgenograms of the pancreatic region showed a row of shadows, slightly larger than a pea, scattered along the course of the pancreas from the caput to the cauda. A shadow as large as a hazelnut was seen in the head of the pancreas. Cholecystography showed a normal gallbladder lateral to the shadows of the calculi.

Treatment and Course—Immediately after admission the patient was given a test diet consisting of 200 Gm of rye bread, 100 Gm of wheat bread, 75 Gm of butter, 200 Gm of boiled codfish, 250 Gm of broth, 250 Gm of potatoes, 200 Gm of vegetables, 150 Gm of cream, 600 Gm of oatmeal-porridge, 50 Gm of cheese and 3 eggs.

This diet contained 124 Gm of albumin and 136 Gm of fat. After the patient had remained on this test diet for five days, the stools of three days were analyzed (table 2).²

While the patient was on this test diet (twelve days), the total daily intake amounted to 124 Gm of albumin, 136 Gm of fat and 268 Gm of carbohydrates (besides sugar in tea), amounting in all to about 2,872 calories. In the stools he lost 85.3 Gm of fat. As a part of this fat—about 8 Gm—is derived from the secretion of the intestinal tract, the loss of fat then was 77.3 Gm or 724.5 calories. The daily excretion of albumin amounted to 10.7 Gm nitrogen. As the normal excretion of nitrogen may be taken to be about 2 Gm—chiefly derived from the intestinal secretion and the intestinal epithelium, and I take 3 Gm to be its maximal limit—he had an additional loss of 8.7 Gm of nitrogen corresponding to 54.3 Gm of albumin or about 223 calories. He thus had at his disposal 2,872 — (724 + 223), or 1,925 calories, the basal metabolism (normally from 98.1 per cent to 100.6 per cent) would normally require 1,660 calories,³ as the patient's height was 175 cm, his weight, 63.75 Kg and his body surface, 1.75 square meters.

Thus, according to this calculation, there was a balance of 265 calories from the total supply. These calories were disposed of by bowel movements usually twice a day in the process of digestion, and by gain in weight. One would be inclined to expect only a slight gain in weight, but the patient gained 8 pounds (3.5 Kg) in twelve days. It should be mentioned that the stools were formed or only slightly liquid during the patient's four days' stay in the Bispebjerg Hospital. The diuresis was normal, from 1,200 to 2,000 cc.

The patient gained 22 pounds (9.75 Kg) in weight while he was being treated in St. Elizabeth's Hospital. During the last week before his discharge, he gained 1,000 Gm, this gain was made on the same diet with the same supply of calories as that at the time of the first examination of the metabolism. The last gain could hardly be due to retention of water, although the marked gain in weight at the time of the first examination of the metabolism most likely should be attributed to retention of water. This striking faculty of utilizing food contrasts strongly with the extreme waste of proteins as well as fat with a subsequent severe loss in weight, as has been demonstrated in dogs on which pancreatectomy had been performed (Hédon,⁴ Falta, Grote and Staheln⁵). This is suggestive of the theory that the pancreas is of importance as a regulator of the metabolism by means of an internal secretion—an internal secretion which my patient, with the marked impairment of the external pancreatic function, must have preserved intact.

2 Several authors claim that an increased amount of lecithin in the stools is characteristic of the pancreatogenous steatorrhea as contradistinguished from the other forms of abnormal fat excretion, because it was thought (Deucher) that only the pancreatic juice was capable of splitting the lecithin. Apart from the fact that micro-organisms in the intestinal tract also are able to split this phosphatide, the quantitative determination of lecithin is most uncertain. For the phosphatides—especially the lecithin—are unstable compounds and are readily split. Furthermore, there are at least two kinds of phosphatides with one or two phosphorus atoms respectively, this makes it impossible to estimate these substances quantitatively by determining the amount of phosphorus. The quantitative proportion of the two phosphatides varies considerably, and consequently it can simulate an increase or a decrease of the phosphatide content.

3 Calculated as 950 calories to 1 square meter of surface.

4 Hédon and Ville. *Arch. de Physiol.* 9: 622, 1897.

5 Falta, Grote and Staheln. *Hofmeister's Beitr.* 66: 1, 1907.

I should mention one more of the patient's symptoms, namely, mild anemia (hemoglobin 70 per cent) It has been asserted (Mayo Robson,⁶ Deaver⁷ and Chvostek⁸) that pancreatic lesions often are associated with anemia, this is true in about half of Deaver's cases Deaver came to the conclusion that the anemia is a secondary effect of lowered nutrition, while Mayo Robson and, particularly, Chvostek maintained that the pancreatic lesion is the direct cause of the anemia, which can be of a pernicious type In three cases of pancreatic lesion with anemia, reported by Chvostek, one patient presented an anemia which at first was secondary but which became pernicious shortly before death There is, however, no proof that the patient suffered from a pancreatogenous steatorrhea, his condition can just as well be considered nontropical sprue Autopsy was performed in the other two cases, this showed that the pancreatic lesion was complicated with simple anemia Mayo Robson likewise stated that the anemia in chronic pancreatitis can be of a pernicious type, but the evidence he gives is vague He reported the number of red blood corpuscles as being from 3,000,000 to 3,500,000, and the hemoglobin from 50 to 70 per cent To my knowledge, Mayo Robson does not furnish any other evidence of pernicious anemia in chronic pancreatitis Walko reported a case of acute pancreatitis with anemia in which the index was raised, but this case was hardly one of pernicious anemia, it was probably toxic anemia combined with intensive regenerative processes in the bone marrow

In a previous paper,¹ I discussed at greater length the question of anemia in chronic pancreatitis with fatty diarrhea Here I merely wish to say that in the six patients with pancreatogenous fatty diarrhea whom I have examined, only two presented a condition of mild anemia, hemoglobin 77 per cent and 70 per cent (this case), and that the only other abnormality revealed by examination of the blood was a low number of platelets in one case (12,000) and a small but hardly abnormal number of platelets in another case (250,000)

Further, the exceedingly voracious appetite is noteworthy, a phenomenon which I repeatedly have observed in cases of pancreatogenous fatty diarrhea Besides plenty of dinner, cold meats and other food the patient in the present case would eat thirty slices of bread (about 700 Gm) a day A similar strong sensation of hunger was observed in dogs on which pancreatectomy had been performed

An examination of the enzyme content of the duodenal juice showed that the lipolytic enzyme is present constantly in only a slight amount, even in those tests in which the hydrogen ion concentration is most

6 Robson, Mayo *Edinburgh M J* **18** 1905, p 485

7 Deaver *New York M J* **95** 573, 1912

8 Chvostek *Wien klin Wchnschr* **31** 1918, no 5, p 121

favorable to the action of lipase (p_H from 6 to 7). I did not find any similar condition in thirteen normal persons. It is not abnormal that neither tryptic nor diastatic action was observed at the low hydrogen ion concentration 3.44, but the small amount of these enzymes at p_H from 6 to 7.7 is extraordinary. A previous examination showed absence of lipase, a faint tryptic and a normal diastatic action. Thus the amount of diastase varies a great deal, the trypsin is more constant but is present in only a slight amount, the lipolytic action is constantly low, which, I think, indicates a pancreatic lesion. At any rate, these observations agree with the results of the examination of the metabolism.

There can hardly be any doubt that the condition in this case was a typical pancreatogenous fatty diarrhea. The insidious development of the lesion without any previous symptoms from the gastro-intestinal tract, the quickly observed steatorrhea with production of a yellowish oily mass and the marked increase in appetite which explains the relatively small loss in weight, sustain the interpretation of the case. As I have shown, the three cardinal symptoms of pancreatogenous fatty diarrhea are steatorrhea, azotorrhea and permanent or alimentary glycosuria of a diabetic type. The two symptoms first mentioned were present in this case to a marked degree, but I was not able to demonstrate glycosuria. The report of a previous case shows that glycosuria can be absent when this lesion is present, at least in the initial stage of the lesion. A patient previously mentioned (F. N. [no. 5]) was not found to have alimentary glycosuria of diabetic type until one and one-half months after the first examination, when the blood sugar increased to 0.245 per cent. In the present case, however, the blood sugar curve was perhaps not normal, as it showed an unusually slow fall toward the initial value. With the demonstration of a lesion in the pancreas, one may assume that this slow fall is due to a morbid condition of the pancreatic islands.

Finally, the roentgen-ray observations—that is, the shadows of calculi in the pancreas—confirmed the diagnosis.

Nontropical sprue is the only disease that might be considered in a differential diagnosis. The diagnosis of this condition was contradicted in the present case by (1) the pronounced steatorrhea with production of the oily mass, this symptom—to my knowledge—is not met with in sprue, (2) the slight saponification, as the soaps (determined as fatty acids) made up only 5.4 per cent of the excreted fats, (3) the marked azotorrhea in which the elimination of nitrogen was about three times larger than normally, (4) the disturbance of the internal secretion of the pancreas, and (5) the absence of stomatitis, (6) the mild anemia, which was not of a pernicious type, (7) and the absence of disturbances of the gastro-intestinal tract previous to the attacks of fatty diarrhea.

From the objective signs, the fatty diarrhea with azotorrhea and the somewhat abnormal blood sugar curve, one must conclude that a diffuse lesion of the pancreas was present, and that this lesion had attacked the islands of Langerhans as well as acini. I know of only two such diffuse lesions of the pancreas, diffuse carcinoma of the pancreas and chronic pancreatitis. Diffuse carcinoma of the pancreas is a rare condition, and the long duration of the illness excludes the possibility of that lesion in this instance. It therefore must be assumed that this case was one of chronic pancreatitis with extensive calculus formation, as evidenced by the roentgenograms. As far as I know, pancreatic calculi have been demonstrated in every case of more or less advanced chronic pancreatitis in which autopsy has been performed, of course, there has been a great deal of discussion as to whether this calculus formation is the primary process and the cause of the pancreatitis, or vice versa, but the question has not been settled conclusively. Hansen⁹ recently reported a similar case in which autopsy was performed. Still, it is by no means a constant phenomenon that pancreatic calculi involve an abnormal excretion of fat, as is evident from a case reported by Jaquelin and Quénu¹⁰. In my case, however, it seems reasonable to assume that the calculi are contributory—and perhaps markedly so—to the severe impairment of the external function of the pancreas.

On the whole, the causes of chronic diffuse pancreatitis are not well known. As I have pointed out, syphilis is of considerable importance as a cause, then tuberculosis, arteriosclerosis, and, perhaps, formation of calculi, none of the first three possibilities can be taken into consideration in this instance.

For the sake of comparison, I shall mention another case which I reported in the paper previously quoted. The patient was an architect (V. T.), aged 57, who contracted syphilis thirty years previously. He had suffered from constipation since he was 26 or 28 years of age, and since the age of 38 had had colicky pains in the abdomen, these pains were diagnosed cholelithiasis. Fatty diarrhea was noticed one year ago and glycosuria was noted at the same time. The patient was admitted to the Bispebjerg Hospital, where analysis of the metabolism (table 2) showed a daily loss of fat amounting to 132 Gm and a loss of nitrogen amounting to 16.8 Gm. At the time of the patient's discharge from the hospital, the loss of fat was brought down to 21.3 Gm, and the loss of nitrogen to 3.23 Gm. At the same time, he was found to have diabetes with sugar in the urine amounting to as much as 6 per cent, diacetic acid, blood sugar (fasting) 0.296 per cent.

⁹ Hansen, Svend. *Ugeskr. f. Læger* 88:328, 1926.

¹⁰ Jaquelin and Quénu. *Arch. de mal. de l'appar. digest.* 17:384, 1927.

and diuresis 3,000. He improved still more after being discharged, and the color of the feces became normal, but the glycosuria persisted. He died one year later from acute pneumonic tuberculosis. At this time, the stools were a normal color and contained but few dioplets of fat (microscopic examination).

Comparison of this case with the preceding one shows two cases of chronic diffuse pancreatitis which, with regard to clinical symptoms, illustrate the extremes of changes in the fat, protein and carbohydrate metabolism which this disease involves. The last case of relatively quick recovery from fatty diarrhea in a diabetic patient is closely related to that form of diabetes which was called Hirschfeldt's¹¹ pancreatogenous diabetes, and in which the ability to digest fat—sometimes also protein—is lowered, at least periodically, the second case, then, is a case of diabetes in which the inflammation is not localized to the pancreatic

TABLE 3—*Transition Types of Disease Between Two Extreme Types of Pancreatogenous Fatty Diarrhea*

Disease	Internal Secretion	External Secretion
Diabetes	Abnormal	Normal
Hirschfeldt's diabetes	Abnormal	Slightly abnormal
Pancreatogenous fatty diarrhea with azotorrhea and diabetes	Abnormal	Strongly abnormal
Pancreatogenous fatty diarrhea with azotorrhea and alimentary glycosuria of diabetic type	Slightly abnormal	Strongly abnormal
Pancreatogenous fatty diarrhea without azotorrhea, but with alimentary glycosuria of diabetic type	Slightly abnormal	Abnormal
Pancreatogenous fatty diarrhea with azotorrhea and abnormal blood sugar curve without glycosuria	Almost normal	Strongly abnormal
Pancreatogenous steatorrhea with or without azotorrhea, normal sugar metabolism, pancreatic calculi, cancer of caput pancreatis and Vater's papilla	Normal	Abnormal

islands but has extended to the glandular acini as well. The first case, on the other hand, with the marked impairment of the external pancreatic function and the slight damage to the pancreatic internal secretion, forms the transition to the rare cases of steatorrhea (usually not fatty diarrhea) which are due to localized lesions in the head of the pancreas or its surroundings (Vater's papilla). Such lesions cause a purely mechanical obstruction of the pancreatic duct, they usually do not show any sign of damage to the internal secretion. There are several transitions between these two extreme types of pancreatogenous fatty diarrhea, as shown in table 3.

I shall review briefly the disturbances in the digestion of fat, protein, and carbohydrates which chronic diffuse pancreatitis can give rise to, even though it does not always do so. The clinical experience on this point, on the whole, agrees well with the experimental investigations, and it has been demonstrated that this condition may be associated with

an impairment in the digestion of fat sometimes also of protein, while the digestion of carbohydrate (starch) is always normal (Muller,¹² Deucher,¹³ Abelmann¹⁴)

With the experimental results in mind, one would expect chronic diffuse pancreatitis to be more advanced in cases of fatty diarrhea that are complicated with azotorrhea than in those cases in which the digestion of protein is normal. And if one takes an increased loss of fat as an indication of an aggravation of the pancreatic condition, as illustrated in table 4, one finds this to hold true. There is no azotorrhea associated with a relatively small loss of fat, and the azotorrhea is aggravated with the increasing loss of fat.

It is important that the digestion of carbohydrate is sustained to its full extent in pancreatogenous steatorrhea, because it is essential to cover the deficiency in the digestion of fat and protein by an abundant supply of carbohydrates. If the pancreatogenous fatty diarrhea is

TABLE 4—*Relation Between Loss of Nitrogen and Fat in Six Cases of Pancreatogenous Fatty Diarrhea*

Name	Age	Sex	Daily Intake of Fat, Gm	Daily Excretion of Fat, Gm	Loss of Fat in per Cent	Daily Intake of Nitrogen, Gm	Daily Excretion of Nitrogen, Gm	Loss of Nitrogen per Cent
N I†	66	♂	95	13	13 #	15.6	1.65	11
V H	36	♂	98	29.9	30.5	16.2	2.6	16
C J	55	♂	95	56.9	60	15.6	4.3	27.6
J N	46	♂	108	85.4	81.8	18.9	8.9	47
V K*	43	♂	136	101	74.3	19.84	9.63	53.9
V T	57	♂	95	132.5	139.5	17.6	16.8	97

* Results of last examination

† The case reports of patients N I, V H, C J and V T are published in a previous paper (Acta med Scandinav 64:292, 1926)

The result is approximate

complicated with diabetes, the dietetic treatment is complex, for one cannot give the patient large amounts of fats or proteins without aggravating the diarrhea. In most of these cases, however, the diabetes is rather mild and does not require any strict dietetic regimen. In one of my patients (V K) I found, as already mentioned, a lowered ability to digest starch, objective signs of fermentation dyspepsia, starch in the stools, granulose-containing bacteria and increased fermentation, on that account, I endeavored to ascertain how much the ability to digest starch was impaired. The amount of starch in the stools was determined four days in succession, it was found to be, respectively, 0.88, 0.32, 1.16 and 0.20 Gm. This loss must be said to be small, as the total intake of carbohydrates was 268 Gm (J. Mayrhofer's method was used for the quantitative starch determination).

12 Von Muller, F. Ztschr f klin Med 12:45, 1887

13 Deucher. Cor-Bl f schweiz Aerzte 11:321, 1898

14 Abelmann. Inaugural Dissertation, Dorpat, 1890

In the present case there is definite evidence that the pancreas is abnormal, namely, the presence of calculi. Hardly any one would dispute the right to assume that there is a relationship between the pancreatic lesion and the demonstrated disturbances in the digestion of fat and protein. The lowered ability to digest protein is readily understood when one assumes that the secretion of pancreatic trypsin or its hydrolytic power is lower than normally. But for the present I fail to understand the chief symptom of the condition, the fatty diarrhea, I cannot explain why these patients eliminate so much more fat than do normal persons.

In order to make this clear, it is well to review the process of normal digestion and absorption of fat as Pfluger¹⁵ presented it in the beginning of this century, for his view still prevails.

As is well known, the main thought in Pfluger's theory is that the fat must be brought into a water-soluble form in order to be absorbed. The neutral fats of the food are hydrolyzed by the pancreatic lipase and other lipolytic enzymes of the intestinal content into free fatty acids and glycerin. The free fatty acids are dissolved by the bile, and they combine with the alkalis of the bile and the intestinal content (sodium carbonate according to Pfluger) into soaps, which are absorbed. Within the epithelial cells of the intestines, the soaps are converted into neutral fats, as the glycerin likewise is absorbed, either the alkalis are secreted back into the intestinal tract, or they enter the blood stream and are eliminated with bile and pancreatic and intestinal juice, whereafter they again are utilized for saponification. A normal absorption of fat depends largely on the emulsification of the fats, for emulsification makes the fats more susceptible to the action of lipase on account of the larger surface. This emulsification of the alimentary fats is principally accomplished by the bile and the soaps, the pancreatic juice is also said to emulsify fats.

An abnormal elimination of alimentary fats might well be thought to be due to one of the following three causes: (1) defective hydrolysis of the fat on account of an insufficient production or action of the lipolytic enzymes, particularly pancreatic lipase, (2) deficient saponification, and (3) defective emulsification of the fats. It is an obvious conclusion that the cause first mentioned might be the explanation of the steatorrhea in pancreatogenous fatty diarrhea, as the external and internal secretion of the pancreas has been found to be abnormal. But this explanation cannot be accepted as a matter of course, for the greatest number of cases of pancreatogenous fatty diarrhea show a normal or only slightly impaired hydrolysis of the alimentary neutral fats.

15 Pfluger. Arch. f. Physiol. 82: 354, 1900.

I think that the neutral fats in feces rarely amount to so much as was found in the patient in this case at the time of the last examination, the neutral fats being 57.8 per cent of the fecal fats. Gross¹⁶ found as little as from 12.4 to 8.9 per cent, Salomon¹⁷ 9 per cent, and Almagia 7.25 and 4.07 per cent neutral fats in the fecal fat content. Usually the figures are larger, however, varying from about 30 to 40 per cent, that is, hydrolysis is normal or only slightly impaired. Consequently, the cause of the fatty diarrhea cannot be a defective hydrolysis of the alimentary neutral fats, not in most instances at any rate. May it then be explained by assuming that soaps are formed in an abnormally small quantity? This view might appear to be sustained by two facts. In the first place, a large amount of free fatty acids is found in the feces (up to 8.9 per cent of the fecal fat content, Gross) in advanced cases of pancreatogenous fatty diarrhea, in the second place, the amount of soap in the feces in such cases is abnormally small. Still, a defective saponification can hardly be the cause, for one must assume that the bile, the intestinal juice and the pancreatic juice contain alkalis sufficient for the normal extent of this process. Nor is saponification a process which has to be accomplished all at once—no more so than the production of free fatty acids from the neutral fats. The process takes place gradually, as the new-formed soaps are absorbed, alkalis are set free for combination with the hydrolyzed acids.

The fact that the feces in pronounced cases of pancreatogenous fatty diarrhea contain only a small amount of soaps cannot be considered as supporting the view that saponification in the small intestine is abnormally poor, for the fecal soaps are the slightly soluble calcium and magnesium salts, while the soaps absorbed, according to Pflüger, are mainly the soluble sodium soaps. If there were any connection between saponification in the intestines and the fecal soap content, one would expect to find few soaps in acholic steatorrhea, and this is by no means the rule. Calcium and magnesium soaps in feces originate chiefly from the presence of these two metals in the food, and thus they do not have any bearing on the question of the absorption of fat.

As to the last possibility—that the fats or the fatty acids are not emulsified—it is not probable, as Pflüger has shown that the bile is able to make all the hydrolyzed fats water-soluble, and more besides. This explanation then would necessarily be contingent on an abnormality of the bile in pancreatogenous fatty diarrhea, but there is no plausible evidence that this is the case. It is known that in some cases of pancreatogenous fatty diarrhea the liver also can be the site of a chronic inflammation—and this coincidence is most frequent in syphilitic pan-

16 Gross and Guleke. *Die Erkrankungen des Pankreas*, Julius Springer, Berlin, 1924.

17 Salomon and Almagia. *Wien klin Wchnschr* **121** 870, 1908.

creatitis—but in cases of pancreatogenous fatty diarrhea, autopsy usually shows a macroscopically normal liver

In weighing the evidence from an analysis of the fecal fats, I cannot reasonably explain the fatty diarrhea by assuming a defective fat cleavage due to a lowered splitting up of the fats, nor by the supposition of a lowered formation of soaps or of a defective emulsification of the fats. The mere fact that some of the fecal fat in severe pancreatogenous fatty diarrhea is excreted as an oil-like mass, chiefly composed of neutral fat, is not proof of a defective emulsification of the fat in the small intestine. And as the increased peristalsis, which produces diarrhea, does not imply a substantial lowering of the absorption of fat, I thus cannot explain the cardinal symptom of the condition, namely, the fatty diarrhea.

Of course, attempts have been made to explain this peculiar condition, for it is only reasonable that the idea of the pancreatic lesion as the cause of the excretion of fat could not be dismissed. The view first presented is that the fat cleavage found in pancreatogenous fatty diarrhea is due to bacterial action and not—or only in part—to the pancreatic lipase, consequently, a large portion of the fat would pass down into the colon as neutral fat and would not be hydrolyzed until it reached this intestine. Concerning this it may be said that even though intestinal bacteria are capable of splitting neutral fat, this cleavage is rather insignificant, according to von Muller's investigations with adults and Escherich's¹⁸ investigations with children. On mixing feces with neutral fat (milk), von Muller found that the cleavage varied a great deal at 37 degrees, the highest value being about 13.4 per cent of the neutral fat. Schiff, Kochmann¹⁹ and Michaelis²⁰ have investigated various strains of the colon bacillus without being able to demonstrate any lipolytic ferment. It is possible, however, that the small amount of soaps in the feces in cases of pancreatogenous fatty diarrhea might be interpreted as being due to a cleavage of the calcium and magnesium soaps by intestinal bacteria (Alsleben²¹). That intestinal bacteria (bacteria in colon) bear some part in the fat cleavage is probable, as normal persons show a higher percentage of hydrolysis in the fat content of the rectum than in that of the small intestine. Thus Umber and Brugsch²² found that 30.2 per cent of the fat content in a normal man was hydrolyzed in the duodenum, 68.9 per cent was hydrolyzed in the lowest part of the ileum and 81 per cent in the rectum. Ten per cent would then be the maximum of fat cleavage by the intestinal bacteria.

18 Escherich, quoted by von Muller

19 Schiff and Kochmann. *Jahrb f Kinderh* 49 181, 1922

20 Michaelis. *Ztschr f Immunitatsforsch u exper Therap* 36 449, 1923

21 Alsleben, M. *Handb d norm u path Phys* 3 1035, 1927

22 Umber and Brugsch. *Arch f exper Path u Pharmakol* 55 164, 1916

and this figure agrees well with those of von Muller. Abelman found similar proportions in dogs. In order to explain the considerable cleavage of fat in pancreatogenous fatty diarrhea—it may even amount to 95 per cent of the fecal fat content (Gross)—as largely due to bacteria, one must attribute to the intestinal bacteria such a strong lipolytic power as is contrary to all published results of investigations of this question.

Another theory tends to show that the pancreas has an internal secretion which acts on the absorptive faculty of the intestines. The theory was first advanced by Lombroso,²³ and he founded it on the following experimental observations:

If in dogs a pancreatic fistula is produced in such a manner that all the pancreatic juice escapes through the fistula, or if the head and the ducts of the pancreas are extirpated while some of corpus and the tail are left in place, or if the pancreas is extirpated and then implanted in the abdominal wall, these injuries will—according to Lombroso's experiments—lower the absorption of fat from 81 to 44.1 per cent after ligation of the pancreatic ducts, from 11.4 to 22 per cent with Pavlov's fistula and from 22.6 to 73.2 per cent after transplantation of the pancreas into the abdominal wall. If the pancreas is completely removed from the animals operated on in this manner, the loss of fat will exceed 100 per cent.

As Lombroso did not succeed in improving the absorption of fat in such animals by introducing liberal amounts of pancreatic juice into the duodenum, he concluded that the pancreas has an internal secretion which influences the absorptive faculty of the intestines. In a later paper, he further elaborates his theory by demonstrating that dogs on which pancreatectomy has been performed eliminate fat in excess of the intake with a melting point different from that of the fat ingested. Thus the pancreas would be able to transfer fat from the fat depots to the intestines.

Lombroso's experiments, however, have been criticized a great deal first by Pflüger, who considers his determination of the absorption values to be incorrect, and who is unable to subscribe to Lombroso's denial of the presence within the gastro-intestinal tract of secretions which can fill the place of the pancreatic juice. Further, Burchardt²⁴ has not been able to confirm the results of Lombroso's experiments but some observations by Hedon, Luthje, Falta, Grote and Stahelin (references to the literature are given by these authors) on the increased waste of proteins and fats in pancreatectomized dogs support the view that the pancreas is of importance in the protein and fat metabolism—

23 Lombroso, Ugo. *Arch f exper Path u Pharmacol* **56** 357, 1907.

24 Burchardt. *Arch f exper Path u Pharmacol* **58** 251, 1908.

just as it most decidedly is so in the carbohydrate metabolism. Fatta, Grote and Stahelin think that through internal secretion the pancreas secretes a substance which restricts the combustion of fat in normal persons and likewise, to some extent, the protein metabolism. In that respect it is worthy of mention that clinicians speak of a pancreatogenous adiposity. All these investigations, however, merely intimate that the function of the pancreas is more complex and covers more phases than those known so far, namely, its external function and its part in the carbohydrate metabolism, they do not explain why the fat cannot be absorbed in pancreatogenous fatty diarrhea.²⁵

In view of the rather large discrepancies in the results of experiments on metabolism by various authors, after partial or total pancreatectomy (Abelmann, Vaughan Hailey,²⁶ Lombroso, Burchardt, Fleckseder,²⁷ Hédon and Ville, McClure, Vincent and Pratt²⁸), and considering that the same author using the same technique secures such different results with different dogs, one can only agree with Pratt in his conclusion that dogs vary a great deal in their ability to absorb fat after pancreatectomy. Even after total pancreatectomy some animals can absorb a large amount of fat, while others excrete all the ingested fat and more.

I shall briefly mention the anatomic observations in case V T, the history of which has been given. The values obtained in the metabolism tests on this patient are given in table 2 (V T). As already mentioned, the fat and protein metabolism remained almost normal for about one year after the patient's discharge from the hospital, with formed feces of normal color and with few fat droplets in the feces on microscopic examination. The pancreas consisted of a lump of fibrous tissue slightly larger than a hazelnut, corresponding to the head of the pancreas and a coat of fibrous tissue from 2 to 3 mm in thickness enveloping the dilated duct which contained a few calculi ranging in size from that of a pea to that of a millet seed.

Microscopic examination showed that the largest part of the organ consisted of connective tissue with some perivascular round cell infiltration, more marked in the cauda than in the caput, and numerous dilated

25 Hill and Bloor (*J Biol Chem* **53** 171, 1922) have examined the fecal fat content after intake of meat and coconut-oil and have found its melting point to be constant, regardless of the food. According to their opinion, this indicates that fat is not secreted in the intestines, but that the ingested fat normally is completely absorbed, and that the fecal fat content is derived from intestinal juice, bile, leukocytes, etc.

26 Vaughan, Harly. *J Physiol* **18** 1, 1895.

27 Fleckseder. *Arch f exper Path u Pharmakol* **59** 407, 1908.

28 McClure, C W, Vincent, B, and Pratt, J H. *J Exper Med* **25** 381 1917.

secretory ducts Of the glandular tissue, only a few remnants of acini remain in isolated spots and a few evidently hypertrophic islands The specimen weighed 25 Gm (the normal weight of the pancreas is from 100 to 120 Gm)

It is astonishing, to say the least, that such an atrophic pancreas from which the acinar gland tissue has almost completely disappeared should be able to maintain an almost normal absorption of fat But the case is not exceptional Von Muller reports a case of almost complete atrophy of the pancreas in which the digestion of fat was normal and the digestion of protein only slightly impaired, he cites this case as evidence of his view that the pancreas is not of great importance in the digestion of fat In 1925, Labbe²⁹ had a similar case in which the digestion of fat and protein was normal At no time during their sickness did either of these two patients have fatty diarrhea

I cannot get away from the fact that atrophy of the pancreas—just like pancreatectomy in animals—is tolerated differently by different persons, even though this condition usually implies considerable disturbances in the digestion of fat and protein Consequently, some persons are more capable than others of mobilizing their auxiliary digestive ferments and of accomplishing the absorption of their cleavage products But the process is not known It is probable that chronic diffuse pancreatitis with its slow progress gives the organism a better chance of attaining this end than does experimental pancreatectomy It is not surprising that an extensive formation of calculi in the pancreas, as in the case reported here with large concretions in the caput—most likely in Wirsung's duct—is more apt to cause a severe and protracted impairment of the digestion of fat and protein than is the insidious chronic pancreatitis, with less extensive stone formation In the six cases of pancreatogenous fatty diarrhea that I examined previous to this case, the fatty diarrhea was transitory and of short duration (from two months to about one year), and it yielded to suitable treatment In this case it was aggravated

Cases of fatty diarrhea in connection with chronic diffuse pancreatitis, or rarely with a diffuse carcinoma of pancreas—are encountered, but I am unable to explain the origin of its chief characteristic, the abnormal elimination of fat Cases of chronic diffuse pancreatitis in which the glandular structures are almost completely destroyed are seen, and I fail to understand why these cases are not associated with fatty diarrhea, and yet there is no doubt that the pancreas is important to the assimilation of fat in the intestines Finally, one encounters fatty diarrhea in cases in which neither the pancreas, the intestines nor the bile

29 Labbe Arch de mal de l'appar digest 14 581, 1925

appears to be abnormal, namely sprue. I therefore cannot explain the pathogenesis of fatty diarrhea.

Treatment—The metabolism tests showed that it was necessary to restrict the intake of fats and proteins as far as feasible, as a more plentiful supply of these substances merely would increase the diarrhea. The patient gained 22 pounds ($9\frac{3}{4}$ Kg.) by increasing his intake of carbohydrates—plenty of bread (he ate as much as thirty slices of bread a day!), porridges, fruits, vegetables, honey, marmalade and beer—a diet poor in fats and relatively poor in proteins. He again became normal as to body fat. He was given five tablets of 0.5 Gm. of a preparation containing pancreatin with 10 per cent of tannin a day for a period of five days, during which time the daily amount of feces was 670 Gm., in the five days preceding this period the amount was 570 Gm. a day, and in the five days following the discontinuance of pancreon, the administration of the amount was 670 Gm. a day. Pancreon thus did not have any effect on the amount of feces which are composed mostly of fat and undigested or partly digested proteins. Throughout the entire period, the stools were of formed consistency, usually two stools a day. The diet mentioned had the effect that the stools gradually looked more natural. But, as shown on examination, this improvement did not signify that the patient really did digest the fat better than before, it was merely due to the decrease of fats in the diet. On the whole the total daily amount of feces had decreased, during the first fifteen days on this diet, the stools on an average amounted to 650 Gm. a day, during the last fifteen days to 525 Gm. The interval between these two periods was about six weeks.

SUMMARY

Description is given of a case of pancreatogenous fatty diarrhea, caused by a pancreatitis of unknown etiology that was complicated with extensive calculus formation in the secretory ducts.

This case presents two of the cardinal symptoms of pancreatogenous fatty diarrhea, namely steatorrhea and azotorrhea, the third cardinal symptom, permanent or alimentary glycosuria of diabetic type was absent.

The pathogenesis of the fatty diarrhea is discussed on basis of Pflüger's theory.

A case of almost complete atrophy of the pancreas with normal or only slightly lowered fat absorption is mentioned.

The possibility that pancreas contains a substance which influences the absorption power of the intestine by way of the blood, is discussed.

PEPTONE TREATMENT IN BRONCHIAL ASTHMA

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Although the statement may seem somewhat sweeping, it is nevertheless a fact that a study of bronchial asthma has not yet been presented which might reasonably be viewed as conclusive. This must of necessity be true, because the asthmatic state has become so inextricably involved, not only with the question of anaphylaxis, but likewise with theories of desensitization. And since it is recognized that there is still lacking a thorough understanding of the phenomena of shock and sensitization—on which both anaphylaxis and desensitization have a bearing—the ultimate solution must still be sought.

The conviction that immunization to be effective must be carried out by specific means—largely the work of von Behring and Ehrlich—was somewhat shaken more than thirty years ago. It was then that the theory of nonspecific desensitization was first inaugurated.

This was accomplished through the work of Buchner, Romer, Kuhne, Rumpf, Matthes, Bauer and numerous others, who, by both experimental and clinical demonstration with a number of dissimilar substances, seemed to establish the validity of their theory.

As early as 1895, Matthes,¹ in the therapy of tuberculosis, obtained a reaction following the administration of deuterproteose which was similar to, or identical with, the reaction previously considered specific for tuberculin.

Among other pioneers, the name of Rumpf² stands out prominently. On the basis of experimental work done by Buchner, Rumpf treated with subcutaneous injections of a pyocyaneus vaccine a series of patients who had typhoid fever, achieving results as promising as those obtained by Frankel with typhoid vaccine. It was Rumpf who, at this early period, called attention to the phenomenon now termed anaphylactic shock, consisting of chills, sweating and a fall of temperature and pulse rate following these injections. He also noted that the earlier this therapy was administered in the course of the disease, the better the results, and called attention to the state of well-being experienced after the injection.

Again, Ichikawa,³ working independently, reported in 1912, and again in 1914 results just as satisfactory in paratyphoid fever with intravenous injections of typhoid vaccine as he had obtained in typhoid

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1 Matthes, Max. *Deutsches Arch f klin Med* **54** 39, 1895.

2 Rumpf, T. *Deutsche med Wchnschr* **19** 987, 1893.

3 Ichikawa, S. *Ztschr f Immunitätsforsch* **23** 32, 1914-1915.

About the same time, Kraus,⁴ having investigated the splendid work which had been accomplished in the treatment of typhoid with the intravenous use of colon vaccine, applied the same therapy in puerperal infection, septicemia, scarlet fever and plague, obtaining similarly successful results

On these and on additional observations and results, the modern conception of nonspecific therapy has gradually been built. It had been shown that astounding physiologic effects could be produced in human beings as well as experimentally with various nonspecific antigens

Various proteins and protein derivatives have been employed. In 1910, Schmidt had injected milk intramuscularly, Ludke introduced the injection of proteoses or albumoses, and Mittlander employed hypertonic salt solution. Distilled water, small doses of turpentine, colloidal metals, nucleic acid, lipoids, enzymes and numerous other substances capable of producing a general reaction—today known as shock, anaphylactic reaction and allergy—were administered

As a result of these observations and of increased clinical results, a mass of literature has accumulated, setting forth varying views on every phase of this vast question—the phenomenon of the reaction, immunization and anaphylaxis, the efficacy of nonspecific therapy in general and of the proteins in particular (including substances such as milk, gelatin, globulin, enzymes, normal serum, peptone and egg white), the question of dosage, the advantage of various means of administration and numerous other phases

In nonspecific therapy, as in every newer mode of therapy, the success which attended it may have led to overenthusiasm in its employment. It must not be forgotten, however, as Zinsser⁵ has pointed out in his book that the entire problem is still clothed in considerable mystery and is entirely too complex to be dealt with even in a book of that scope

The fact that varying degrees of success have been attained with a particular form of protein in persons suffering from an apparently identical disorder, or in the same subject at different times, has led therefore to much consideration by various investigators. And it is perhaps through an analysis of their deductions that a solution of the problem may eventually lie

Petersen⁶ states that "protein therapy offers a possibility, perhaps the most powerful at our command, for the alteration of the current of cellular activity, either in the direction of acceleration of function or

4 Kraus, cited by Petersen (footnote 6)

5 Zinsser, Hans. *Infection and Resistance*, New York, Macmillan Company, 1923

6 Petersen, W. F. *Protein Therapy and Non-Specific Resistance*, New York, Macmillan Company, 1923

depression of function," but he admits that its application should be limited to certain stages of the disease process. In this connection, he states

If nonspecific therapy is after all merely a method that deals with heretofore known reactions, we must be prepared to accept the probability that it obeys all the commonly observed laws of biologic reactions. If we regard it as a method of stimulation—plasma activation—it follows that it can only be effective when the protoplasm is still in fit condition to respond to stimulation. Once the stage of exhaustion has been reached, the mere irritation of the nonspecific agent is no longer able to bring about any alteration in the disease process other than aggravation.

Many believe, with Petersen, that the patient does not become sensitized to the proteose injections, but that in this way a degree of tolerance is established in which subsequent injections do not give an equal response. Likewise, Novy, de Kruif and Novy⁷ are of the opinion that peptone itself is not toxic, but when brought into contact with a reactive serum or plasma it brings about the change which results in anaphylatoxin production.

Karsner and Ecker,⁸ in a study of the desensitized state in serum anaphylaxis, tell that "nonspecific, usually transitory reduction of shock, has been produced by an injection of various substances, but the final issue as regards specificity of this phenomenon is still a matter of considerable dispute." These investigators quote Thomson,⁹ who believes that much depends on the degree of sensitiveness in each subject as well as on the particular time of desensitization. They also cite Massini¹⁰ who, following much experimental work, concludes that anaphylaxis is specific, but that, in addition, there is present a nonspecific element. This latter theory is also sponsored by Schiff¹¹ and others.

The theories referred to will no doubt suffice to indicate the general lack of agreement on the subject under consideration in the present article.

VARIETY OF PEPTONE

In regard to the variety of peptone employed in the treatment of patients with asthma, it seems logical to expect that the chemical composition of the particular brand administered would exert a definite characteristic influence. Such, however, does not seem to be the case, as will be noted from the following reports gathered from the literature.

Novy, de Kruif and Novy,⁷ using Witte's peptone, found it less toxic than agar when employed experimentally. In 1927, Auld¹² reports

7 Novy, I. G., de Kruif, P. H., and Novy, F. O. *J. Infect. Dis.* **20**: 657, 1917.

8 Karsner, H. T., and Ecker, E. E. *J. Infect. Dis.* **30**: 333, 1922.

9 Thomson. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **26**: 213, 1917.

10 Massini. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **27**: 194, 1918.

11 Schiff, Nathan. *Am. J. M. Sc.* **5**: 664, 1918.

12 Auld, A. G. *Brit. M. J.* **1**: 829 (May 7) 1927.

unfavorably on results obtained when this brand of peptone was used exclusively, for the reason that it contains histamine. He found several other peptones "dangerous," and others "feeble, as they contain little proteose."

In 1923, Larsen, Haigh, Alexander and Paddock,¹³ on the basis of the success previously (1920 and 1921) reported by Auld in the treatment of bronchial asthma with intravenous and intramuscular injections of a mixture of Witte's and Armour's peptone suspended in 0.85 per cent solution of sodium chloride employed Auld's method in a study on experimental animals. This therapy, as reported by these writers, not only yielded poor response but led them to conclude that "clinically the use of peptone intravenously, in bronchial asthma, according to the method of Auld, has been disappointing, and is considered dangerous."

Among numerous other workers, Miller and Raulston,¹⁴ in 1923, and Ball,¹⁵ in 1927, reported results obtained with intravenous injections of a 5 per cent solution of Armour's peptone in the treatment of patients with migraine. These writers believe that migraine, epilepsy, asthma, hay-fever, urticaria and angioneurotic edema are kindred disorders, all being evidences of anaphylaxis, among other observations they report the presence of eosinophilia in each of the conditions mentioned. Miller and Raulston state, furthermore, "that relief from peptone was temporary as in hay-fever and asthma." In Ball's cases, 15 per cent of the patients showed improvement, 35 per cent were markedly improved and 50 per cent were failures. Miller and Raulston's results approximated Ball's, with 16 per cent improved, 36 per cent markedly improved, and failures in 48 per cent of cases. Miller and Raulston, however, also quote Auld¹⁶ who pointed out the special advantage of Armour's 5 per cent preparation over Witte's, the former containing a smaller amount of primary proteoses. Again, Miller and Raulston suggest that its action as a desensitizer may be due to the proteoses and not to the peptone itself, pointing to the fact that Auld could not secure favorable effects in asthma when pure peptone was administered. Peptone had a definite action in temporarily relieving migraine attacks in their experience, but noting the observations of other workers who reported marked urticaria following single injections, they ventured to suggest that "different preparations of the same brand no doubt differ in their composition."

Whether or not this last feature is an important phase of the subject, contributing to the unreliability of results, or whether still more momen-

13 Larsen, Haigh, Alexander and Paddock. *J. Immunol.* 8:409 (Sept.) 1923.

14 Miller, J. L., and Raulstone, B. O. Treatment of Migraine with Peptone, *J. A. M. A.* 80:1894 (June 30) 1923.

15 Ball, F. E. *Am. J. M. Sc.* 173:781 (June) 1927.

16 Auld, A. G. *Brit. M. J.* 1:696 (May 14) 1921.

tous factors intervene, remains an open question. Much discussion has also centered about the questions of dosage and the mode of administration.

DOSAGE AND MODE OF ADMINISTRATION

Petersen⁶ states

With nonspecific therapy, as with other new therapeutic procedures, there is still some uncertainty as to the proper dosage. Especially is this true because the dosage depends to some extent on the vigor of the patients, on the type of infection which is causing the disease, as well as on the stage of the disease.

On the basis of the fact that in antianaphylaxis or desensitization a nonspecific element is at times observed, other methods have been devised which are sometimes applied more easily than the specific method that Walker has used. Only larger clinical experience will enable us to draw conclusion. It must be borne in mind, too, that our conception of protein therapy must not be limited to the intravenous injection of typhoid vaccine or peptone. Many of the milder reactions continued over a longer period of time may be found much more effective.

Auld reports on the use of injections of peptone (dissolved in physiologic solution of sodium chloride to which a small amount of sodium carbonate is added) given either intravenously or subcutaneously. Pagniez and Widal, Abram and Brissaud use peptone by mouth, and Cordier uses enemas of peptone. Some require the continuous use of the peptone, others do better when it is given for from three to eight days followed by an interval of the same length.

On the whole, the administration of peptone has been accomplished by different routes, each method in turn being advocated or discarded by the various investigators. Pasteur Vallery-Radot and Blamoutier¹⁷ following a three years' experience with peptone, believe that intradermal injections are beneficial in cases of hay-fever and essential asthma in which the attacks are frequent. They advise that this treatment be administered during the attack. Patients with spasmodic coryza improved, although relief was of short duration. These writers administered either Witte's or Chassing's peptone. (The technic and dosage will be described toward the end of this article.) The entire series consisted of twenty injections, administered once a day. Care was exercised to inject the solution into the skin, injected beneath the skin, a phlyctena and sloughing may ensue, according to these observers.

In connection with subcutaneous injections of peptone, Schiff¹¹ reports splendid results clinically with a 33.33 per cent solution of Armour's dry peptone. Three minims (0.18 cc.) of this solution he believes to be a safe dose. This was increased by 1 minim (0.06 cc.), up to 1 cc., at biweekly or triweekly intervals. Schiff, guided by experience, gauges the dosage according to the symptoms and progress of the

¹⁷ Vallery-Radot, Pasteur, and Blamoutier. Bull. et mem. Soc. méd. d. hôp. de Paris **51**: 491 (May 5) 1927.

individual case In the event of a severe local reaction, he repeats the preceding dose Early recognition of the approach to the limit of tolerance is regarded as of great importance

Walker,¹⁸ however, reports that benefit was not derived in a few non-sensitive asthmatic patients, from large doses of peptone, also administered subcutaneously Walker states in this connection

This method of treatment is dangerous unless the patient is tested with peptone to rule out the possibility of his being sensitive to it We feel that this fad of injecting patients with proteins to which they are not already sensitive is, in general, apt to be a mistake

Larsen, Haig, Alexander and Paddock¹³ administered peptone (Chapotaut's peptone tablets) by mouth in a few cases of bronchial asthma, but with negative results It was equally disappointing in patients with urticaria, who were given these tablets in doses of from 0.1 to 0.3 Gm fifteen minutes before meals

In their search for a satisfactory method, Larsen, Haig, Alexander and Paddock thereupon employed the technic used by Auld in this earlier work (20, 16) which consisted of administering intravenously a 5 per cent suspension in 85 per cent solution of sodium chloride, of a mixture of Armour's and Witte's peptones, in ratio of 3:1 Here again, they report that "clinically the use of peptone intravenously in bronchial asthma, according to the method of Auld,¹⁹ has been disappointing and is considered dangerous"

Novy, de Kruif and Novy,⁷ in an experimental study in which Witte's peptone was injected intravenously, found that the symptoms and conditions of guinea-pigs and white rats so treated were identical with those produced by anaphylatoxin, by agar, or by specific anaphylactic shock The average lethal dose for guinea-pigs they report as 0.3 Gm per kilogram, that for the rat being 2 Gm per kilogram—an amount seven times larger than for guinea-pigs In rabbits, in addition to the usual symptoms, such as dyspnea, spasms and convulsions, a striking exophthalmos was noted, also a great drop in blood pressure and a marked decrease in coagulation time The rabbit was found more resistant than the rat, the least amount of peptone which was fatal being 3 Gm per kilogram These animals showed an immunity or tolerance to repeated injections of peptone, the same as shown on dogs and guinea-pigs

These investigators, making additional experimental studies, tested the effect of injecting the animal's own serum treated with peptone and found that here also anaphylatoxin is produced The transfusion of the

¹⁸ Walker, cited by Petersen (footnote 6)

¹⁹ Auld, A. G. Brit. M. J. **1** 576, 1920

blood of rats injected with peptone demonstrated that anaphylatoxin was formed *in vivo*

In 1927, Auld, finding that the effect of peptone in human beings varies greatly, decided on the combined use of peptone, serum and agar in those cases which did not yield to peptone alone. He stated that while these substances "act in an entirely different manner, yet they bring about in animals the same result." Five cases are cited illustrating the splendid effects of this means of therapy in subjects previously treated with little or no success, either with peptone exclusively or with other treatment. Auld, however, admits that a few of his patients—a small percentage—did not respond to this newer therapy.

REPORT OF CASES

Based on the observations cited, I have employed various preparations of peptone, administered in accordance with numerous methods suggested. The entire series comprises sixty cases, grouped according to the following plan:

GROUP 1—Intramuscular injections of a 5 per cent peptone (Armour's) solution, twice a week, for two months.

GROUP 2—Intramuscular injections of a 5 per cent peptone (Armour's) solution, every day, for two weeks, then once a week, for two months.

GROUP 3—Intradermal injections of a 30 per cent peptone prepared according to the method suggested by Dr. Pasteur Vallery-Radot and Blamoutier.²⁷

Fifty grams of peptone are mixed with an amount of distilled water sufficient to make up 100 cc, this is then stirred with a glass rod. It is left at room temperature or put in a water bath, stirring from time to time, and adding water to keep the quantity at 100 cc for from twenty-four to forty-eight hours. It is then filtered through ordinary filter paper, this procedure taking several hours. The solution is put in ampules and sterilized. One cubic centimeter of this solution contains 0.5 grains of peptone.

The first injection consisted of 0.1 cc of the solution, the second, 0.2 cc, the following, 0.3 cc. The last dose was never exceeded. The entire series consisted of twenty injections, one administered each day.

GROUP 4—Peptone powders by mouth in 5 and 10 grain (0.32 and 0.65 Gm) doses, three times a day, one hour before meals, for two months.

GROUP 5—Intravenous injections of 1 cc of 5 per cent peptone solution, twice a week, for four weeks.

GROUP 6—Intravenous injections of 2 cc 5 per cent peptone solution, once a week, for four weeks.

GROUP 7—Intravenous injections of peptone serum, according to the technic suggested by Auld, once a week, for four weeks (on five patients), and once a week for eight weeks (on five patients).

The results in the foregoing cases are as follows:

In groups 1, 2 and 3, ten cases each, benefits did not result. In group 4, there were also ten cases, in which benefits were not noted.

In group 5, five cases, slight temporary improvement was observed, but not sufficient to justify treatment. In group 6, five cases, there was slight improvement following each injection. In group 7, in which injections were given five patients for four weeks and five patients for eight weeks, respectively, benefits were not noted.

As will be seen from this study, the employment of peptone in the treatment of patients with bronchial asthma has been wholly disappointing in my series of cases. In evaluating this means of therapy, I heartily endorse the summarization of Dr. William S. Thomas²⁰ in a recent publication comprising a study of asthma, in which he says:

Careful trial of various nonspecific protein methods of treatment of asthma has left me unconvinced of their value. It is difficult to explain the fact that peptone, for example, as a desensitizing agent and remedy for asthma is approved by English, French and some American writers, while almost all colleagues of my acquaintance, and I with them, have failed to obtain beneficial results from its use, either by the employment of methods of injection or by mouth administration.

SUMMARY AND CONCLUSIONS

After a careful and absolutely unbiased analysis of patients treated with peptone, I feel justified in stating that in my experience peptone is of no value in cases of bronchial asthma.

I hesitate to state this conclusion, in lieu of the favorable result published by such excellent observers as Pasteur Vallery-Radot, Blamoutier, Auld, Schiff and others.

47 West Fifty-Fourth Street

20 Thomas, W. S. *Asthma*, New York, Paul B. Hoeber, 1928.

CHEMICAL ANALYSES OF BLOOD IN PATIENTS HAVING SENILE CATARACT*

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A study of the chemistry of the blood in patients suffering from senile cataract was undertaken because we felt that since this type of cataract is always bilateral, it must be due to systemic changes. It was thought that changes in the blood might possibly point out lines of study which would eventually lead to a discovery of the etiology of these senile changes so frequently seen in the crystalline lens.

As far back as 1881, Cahn,¹ in Hoppe-Seyler's laboratory, following some earlier observations of Jacobsen, reported data on the composition of cataractous lenses, in comparison with those of normal eyes. In lenses exhibiting cataractous changes the figures show a marked increase in all lipids—cholesterol, lecithin and fats. The increase in cholesterol is particularly striking, being 0.62 per cent per hundred parts of the solid residue in normal lenses and 6.22 per cent in cataractous lenses.

In the series of cases studied, the analyses included cholesterol, urea nitrogen, sugar and hemoglobin; a number of other determinations were also made which are not recorded here, namely on uric acid, chlorides, calcium, inorganic phosphates, carbon dioxide content and the p_H , all of which were found to be essentially normal.

Since hypercholesterolemia is encountered in diabetes and in certain forms of nephritis, the figures for blood sugar and urea nitrogen are recorded as bearing on these possible complications.

Cholesterol was estimated by the Myers-Wardell method, blood sugar according to Folin-Wu, urea nitrogen by a nesslerization technic and hemoglobin by employing a Newcomer disk—all as described by Myers' text.²

Strictly normal figures for the cholesterol content of human whole blood may be given as varying from 140 to 170 mg. per hundred cubic centimeters. It will be noted that twenty-nine, or 54 per cent, of the

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1 Cahn, A. Zur physiologischen und pathologischen Chemie des Auges, *Ztschr. f. physiol. Chem.* 5:213, 1881.

2 Myers, V. C. *Practical Chemical Analysis of Blood*, ed. 2, St. Louis, C. V. Mosby Company, 1924.

fifty-four cases in our series show figures for cholesterol above 170 mg. Nine of the cases have figures for urea nitrogen varying from 20 to 23 mg, while three cases show blood sugars above 150 mg. There does not appear to be any direct relationship, however, between the level of

Blood Analyses in Patients with Senile Cataract

	Case	Age	Sex*	Date	Hemoglobin Gm	Nitrogen mg to 100 Cc			Remarks
						Urea	Sugar	Cholesterol	
1	A B	65	♂	2/ 9/27	11.7	12.9	107	519	Old trachoma
2	W W	82	♂	5/17/27	15.3	15.5	99	311	
3	J C	65	♂	7/ 1/27	13.2	11.5	91	261	
4	J H	65	♂	2/24/27	16.5	17.3	87	212	Mild diabetes
5	N F	69	♀	7/15/27	10.8	11.5	90	238	
6	J Mc	57	♀	12/ 7/26	12.4	15.8	113	221	
7	J M	47	♂	11/11/26	14.6	19.9	99	224	
8	M C	80	♂	3/31/27	15.3	12.2	139	218	Diabetic
9	M H	67	♂	6/10/27	12.7	14.4	105	206	
10	A L	65	♂	3/ 2/27	14.3	13.1	303	201	Diabetic
11	G M	72	♂	12/ 9/26	16.5	21.9	105	200	
12	L R	82	♂	7/13/27	15.2	19.5	115	200	
13	H A	84	♂	10/28/26		15.3	104	200	Stone in kidney
14	L S	74	♂	5/20/27	13.5	14.9	92	193	
15	F B	72	♀	6/30/27	15.2	21.8	84	190	
16	A F	71	♂	9/30/26		22.9	121	190	
17	W W	61	♂	7/20/27	12.8	13.8	105	188	
18	M K		♂	6/ 7/27	13.2	17.1	131	181	
19	J R	53	♂	12/11/26	14.5	18.5	85	183	Arteriosclerosis
20	D L	57	♂	9/30/27	15.2	22.2	89	182	
21	G S	58	♂	1/17/27	13.2	17.7	96	180	
22	L M	59	♂	6/ 8/27	15.2	13.3	107	179	
23	N S	52	♂	1/28/26	12.9		94	179	
24	G M	42	♂	6/15/27	15.1	10.1	100	178	
25	A C	67	♂	1/27/27	12.7	7.6	109	177	Adenomatous goiter
26	D D		♂	11/ 3/26	13.2	8.3	116	177	
27	F L	76	♂	1/ 4/27		14.7	111	174	
28	F J	17	♂	10/ 6/26	14.1	15.2	84	174	Complicated cataract
29	C C	58	♂	3/31/27	12.9	16.9	103	172	
30	M M	71	♂	10/ 5/26	13.4	13.5	98	170	
31	D C	62	♂	10/15/26	12.3	14.5	99	167	
32	P B	75	♂	11/ 3/23	12.3	15.9	99	167	Arteriosclerosis
33	M M	57	♂	11/30/26	15.2	11.9	105	167	
34	T E	79	♂	11/ 3/26	13.5	21.9	177	163	
35	H M	46	♂	10/ 8/26	11.2	16.6	88	163	
36	A H	68	♂	1/25/27	13.3	10.3	100	161	
37	P R		♂	3/ 9/27	17.3	12.4	107	160	
38	W W	72	♂	1/ 8/27	13.8	19.0		159	
39	M Mc	66	♂	1/28/27	12.7	17.0	82	158	
40	S T	72	♂	10/ 4/26	13.6	10.6	101	157	
41	J S	65	♂	12/10/26	14.4	22.2	153	156	Diabetic
42	H K	82	♂	4/15/27	11.5	18.0	139	154	Goiter (colloid)
43	B L	51	♂	2/23/27	12.7	12.7	90	151	
44	L O'B	65	♂	5/ 9/27	16.9	13.6	181	152	Diabetic
45	M C	70	♂	10/22/27	11.7	11.6	90	151	
46	H L	43	♂	4/13/27	11.1	14.0	101	148	
47	R R	76	♂	10/ 5/26	14.1	15.5	99	147	
48	L U	65	♂	1/ 6/27	12.1	11.0	98	144	
49	M P		♂	3/ 9/27	12.3	19.8	109	140	
50	J O	50	♂	5/11/27	13.5	9.5	98	132	Old chorioretinitis
51	A N	70	♂	5/ 4/27	16.0	15.4	93	130	
52	G J	88	♂	1/20/26		19.1	105	128	Arteriosclerosis
53	A B	80	♂	1/21/27	14.2	13.1	92	127	
54	W J	52	♂	12/12/26	13.9	15.2	105	121	

* In this column, ♂ indicates male, ♀, female

the blood urea or sugar and the cholesterol, and it does not seem that the hypercholesterolemia may be ascribed to a renal or diabetic factor.

The observations on the blood cholesterol in patients with senile cataract are somewhat analogous to those in cholelithiasis, where efforts to show a direct relationship between hypercholesterolemia and cholelithiasis have been unsuccessful.

thiasis³ have been disappointing in that, at the time of operation, a fairly large percentage of patients show perfectly normal figures for cholesterol, while in many others the hypercholesterolemia observed is due to jaundice. The presence of hypercholesterolemia at the time of the formation of gallstones, however, has never been disproved.

We believe that the rise in the cholesterol content of the blood observed in our series of cases is interesting, but we do not wish to place undue emphasis on it at the present time, although it may well be an important etiologic factor. One of us is now engaged in a study of the blood in noncataract cases in patients of similar age, and is extending the blood studies to cover the fat and lecithin, a study of the tolerance for sugar in patients having senile cataract is also being made. A study of the chemical make-up of cataractous lenses as compared with normal ones is also being undertaken.

Several analyses of lenses, made by Mr P W Salit at our suggestion, are of interest. A normal lens showed 0.4 per cent cholesterol, whereas two cataractous lenses gave figures of 0.51 and 0.7 per cent with blood cholesterols of 0.166 and 0.205 per cent, respectively.

CONCLUSIONS

Chemical blood analyses have been made on a series of fifty-four cases of cataract. The observations on the blood were essentially normal except for the cholesterol, which was somewhat increased in 54 per cent of the cases. This observation is being further investigated.

³ Gorham, F D, and Myers, V C. Remarks on the Cholesterol Content of Human Blood, *Arch Int Med* 20: 599 (Oct) 1917.

PRESENILE DISTURBANCES OF BLOOD PRESSURE ¹

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Clinical experiences give evidence that about the end of the fourth decade of human life, and sometimes earlier, a period begins which may be regarded as presenile age,¹ and it is characterized by disturbances of the circulatory system besides many other alterations. The clinical symptoms of these disturbances are as follows. The blood pressure becomes higher on a constant level, and at the same time one finds various signs of cardiac incompetence, especially during physical work, such as increase in the pulse rate, precordial uneasiness and, sometimes, dizziness. The accommodative power of the blood pressure becomes unsteady, as demonstrated by its irregular fluctuation. Therefore, an investigation into the complicated mechanism of the origin of high blood pressure in persons of presenile age is justified. The problem is important, since it is connected with many interesting questions of disease in human beings.

The consideration of these questions may also bring out some practical points relating to the problems of hygiene, prophylactic medicine, life insurance, etc.

CRITICAL REVIEW OF METHODS FOR DETERMINATION OF BLOOD PRESSURE

Careful determinations of the blood pressure reveal many important data relating to the function of organs which regulate the blood pressure level. Functional changes in this system are often expressed by variation in the blood pressure level, as demonstrated by the investigations of Fahrenkamp,² who found interesting alterations by repeated measurements made during a day, and especially by measurements made early in the morning. C. Muller³ and Katsch and Pansdorf⁴ observed a striking diminution in the blood pressure of normal persons during

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1 This age corresponds to presenile age in my country and, I believe, in all Europe. Possibly it begins somewhat below or above this age in other parts of the world.

2 Fahrenkamp, K. Ueber Hypertension, *Ergebn d ges Med* **5** 144, 1925.

3 Muller, C. Die Messung des Blutdruckes am Schlafenden, *Acta med Scandinav* **55** 381, 1921.

4 Katsch, G, and Pansdorf, H. Die Schlafbewegung des Blutdruckes, *Munchen med Wchnschr* **69** 1715, 1922.

sleep All these observations, however, do not give one sufficient knowledge of the accommodative power of the system which regulates the blood pressure level—the vasomotor center, vasomotor nerves, etc—but prove only the temporary differences in pressure Therefore, one must look for functional tests

By means of functional tests one can determine how certain organs or groups of them react to a certain amount of work, which is the function of the respective organs Pharmacologic tests have been employed as a functional method in determinations of blood pressure, but the drugs used—epinephrine hydrochloride, caffeine, etc—act on the involuntary nervous system, and are not a reliable means for judging the function of organs, since the involuntary nervous system often responds with a twofold reaction (Baráth⁵) More reliable functional methods, therefore, must be obtained I have found that my “labor test” and “psychic test,” as established in previous papers,⁶ are reliable for this purpose

LABOR TEST OF BLOOD PRESSURE

It is well known that physical work is accompanied by a slight elevation of the blood pressure, which is of short duration, and often gives place to a slight decrease of the blood pressure The elevation of the blood pressure and its duration can provide useful information regarding the state of the circulatory system, as shown by the investigations of Schrumpf⁷ In cases of circulatory incompetence, he found that elevation of the blood pressure, associated with an increase in the pulse rate, occurs for a long period of time I observed later, in several patients, in whom there were no signs of circulatory insufficiency, a longer duration of the elevation of blood pressure after work without a persistent tachycardia The explanation of this observation may be that in these cases the regulating mechanism of the blood pressure system is diminished in other words, the regulating system has lost the power of compensating the hypertension caused by labor within a definite period Apparently, the hypertension due to labor remains at a higher level much longer than it does under normal conditions

In considering these preliminary experiments, I found the basis of the labor test, which is carried out as follows The blood pressure of the patient is measured in the early morning hours, before breakfast, in a period of absolute rest Then he is allowed to walk up two flights

5 Baráth, E On the Amphotropic Effects of Drugs upon the Vegetative Nervous System, *Am J M Sc* **172** 107 (July) 1926

6 Barath, E Arterial Hypertension and Physical Work, *Arch Int Med*, to be published

7 Schrumpf, P *Klinische Herzdiagnostik*, Berlin, Julius Springer, 1919

of stairs at a slow pace—in from two to three minutes. The blood pressure is measured immediately after his walk upstairs and then every half minute for from ten to fifteen minutes. The data obtained are registered in a curve. The experiment is repeated some days later under the same circumstances. Three curves of normal young persons are recorded in chart 1.

Usually the elevation of the blood pressure is of short duration, the hypertension due to labor usually varies from 15 to 26 mm (according to the Riva-Rocci sphygmomanometer), and lasts usually from two to three minutes. It is regularly followed by a slight decrease to below the normal pressure.

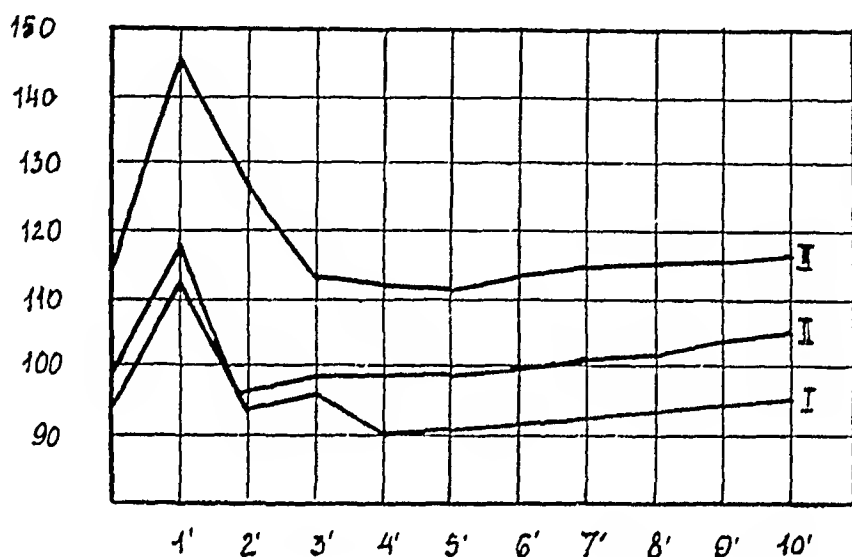


Chart 1—Blood pressure curves of three normal young persons after labor test

I believe that determination of the blood pressure curves after the patient has performed physical work gives a reliable method for testing the function of the regulating mechanism of the blood pressure.

PSYCHIC REACTION OF THE BLOOD PRESSURE

Psychic excitement often produces an elevation of blood pressure, as the experiments of numerous authors have demonstrated. The increase in the blood pressure varies from 10 to 40 mm, according to the intensity of the excitement. The important rôle of psychic factors in the pathogenesis of arterial hypertension, therefore, must be taken into consideration. Emotions of long duration may often cause a more or less permanent elevation of the blood pressure level, as described in various papers dealing with the hypertension.

The simple test I have worked out for the determination of the psychic reaction of the blood pressure is as follows. In the early morning hours, repeated measurements are made of the blood pressure while

the patient is kept in complete physical and psychic rest. Then he is told that he is going to receive an intravenous injection which will be a little painful. A slight elevation of the blood pressure usually follows this declaration.

We give then 1 cc physiologic sodium chloride solution intravenously, in consequence of which the blood pressure increases rapidly, the highest level is reached just after the injection (within two minutes), and then there is a slight but rapid decrease. In normal persons, the elevation of the blood pressure amounts to from 8 to 15 mm, as measured by the Riva-Rocci sphygmomanometer. Three curves of normal young persons are presented in chart 2.

The form of these curves is subject to many variations, depending on the excitability of the patient, hence, they must be interpreted with great caution. In pathologic conditions, however, they may be of great diagnostic value.

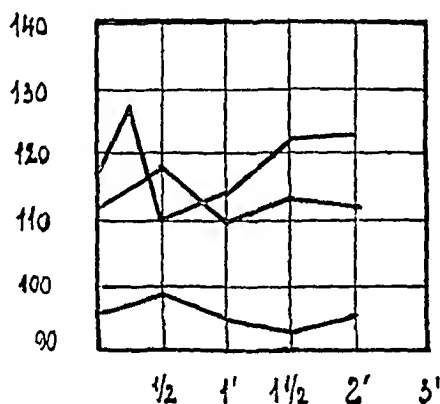


Chart 2—Blood pressure curves of three normal young persons after psychic test

PRESENILE FLUCTUATION OF BLOOD PRESSURE

The systolic pressure of persons, aged from 45 to 55, in my country is usually from 110 to 140 mm, as determined by the Riva-Rocci sphygmomanometer in a large series of cases. These values were recorded in the early morning. They must be regarded as a little elevated, the normal values in young persons being somewhat less (usually about 100 mm). A striking diurnal fluctuation of the blood pressure often occurs in the presenile period. A comparison of the blood pressure measurements made early in the morning and with those made during the day or evening shows the changes illustrated in chart 3.

This inconstancy of the blood pressure is similar to that found in the patients suffering from essential hypertension who were described in the papers of Fahrenkamp² and Kylin⁸. The majority of my patients

⁸ Kylin, E. Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926

however, apparently were healthy. Only a few of them had the symptoms described by Wenckebach in his report on the "50 years old man"—headache, dizziness, precordial uneasiness, palpitation, etc.

It has been a common observation in the roentgen-ray examination in my patients, that the majority of elderly men have a distinct enlargement of the aorta, often without any sign of cardiac disturbance. In some cases, however, the foregoing slight symptoms were probably caused by aortic alterations, especially in persons who had worked excessively or had led a hurried, worried life.

LABOR TEST IN PATIENTS OF PRESENILE AGE

The most important disturbance in the regulation of blood pressure can be detected by means of the new methods described previously.

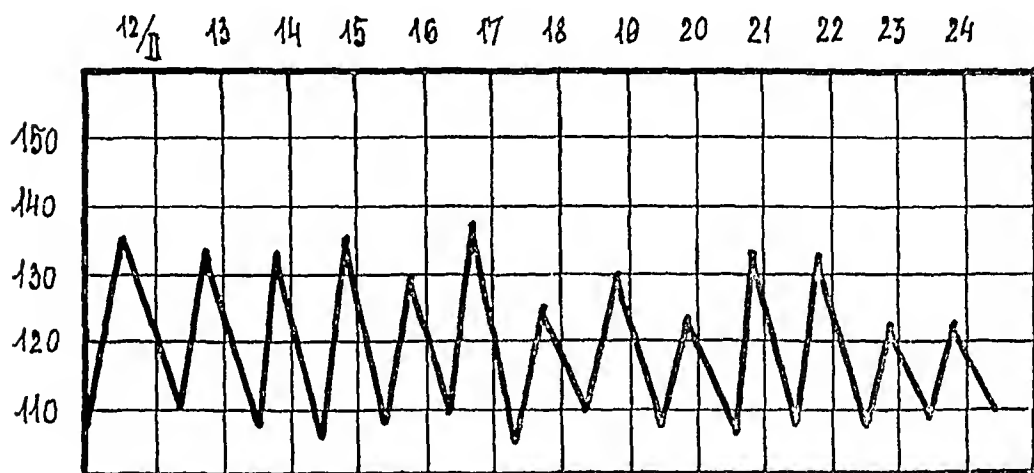


Chart 3—Comparison of blood pressure measurements made in early morning with those made during the day or evening

These tests show that the fluctuation of the blood pressure in elderly persons is caused chiefly by a diminished compensating power of the regulating mechanism. In this way, the otherwise transitory elevations may become permanent.

Determinations of blood pressure curves after work has been performed show remarkable differences in elderly and in young persons. This is pictured in the curves of older persons in chart 4 and in the normal curves of young persons in chart 1.

In examining the three curves in chart 4, one finds that the first difference is in the descending portion of the curves. The duration of the elevation of the blood pressure is much longer than it is in younger persons, so that the blood pressure reaches its former level later. The descending portion of the curves is elongated. Contrary to observations in the reaction type of young persons, the elevation of the blood pressure is not only of longer duration but also much higher. The increase of the

blood pressure is between 30 and 60 mm, as determined by the Riva-Rocci sphygmomanometer, and it lasts longer than from three to five minutes. Moreover, subnormal pressure was not found after the elevation as it is in younger persons. Latent disturbance of the regulating mechanism of the blood pressure thus becomes evident as a result

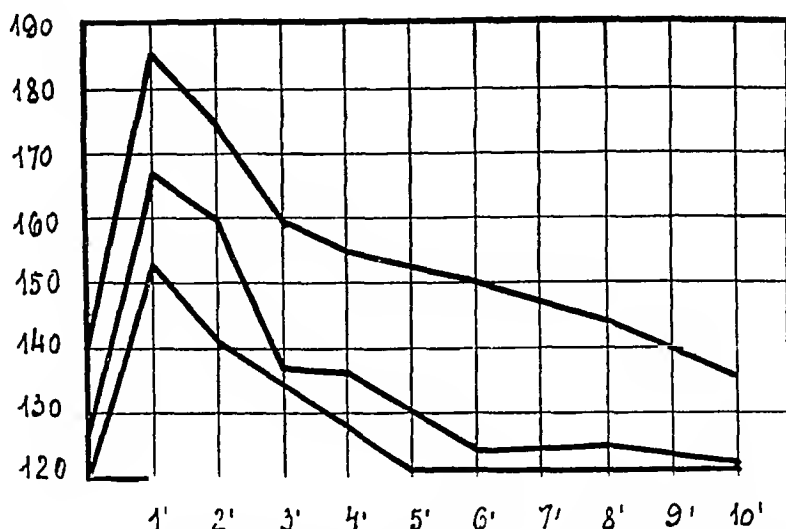


Chart 4—Blood pressure curves of elderly persons after labor test

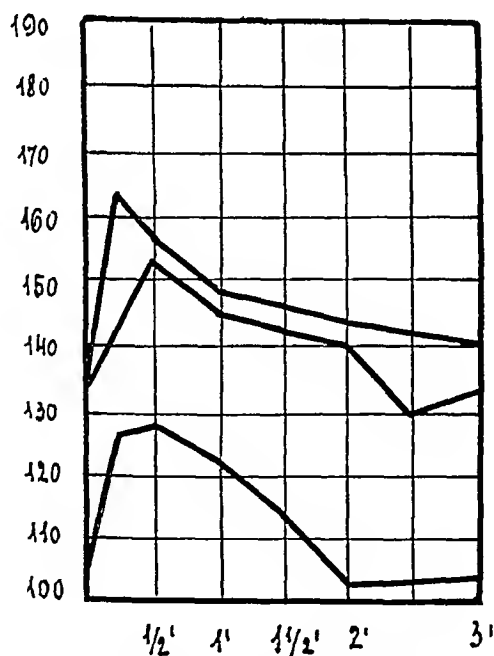


Chart 5—Blood pressure curves of elderly persons after psychic test

of the labor test. The compensating powers, which in young persons cause the transitory elevation of the blood pressure to return rapidly to the normal level, are deficient in the presenile period, they act slowly and late. This behavior of the blood pressure curves is an important sign of beginning disturbances of the regulating mechanism.

PSYCHIC TEST IN PATIENTS OF PRESENILE AGE

Conclusions similar to those drawn from the curves obtained in labor tests may be reached in an examination of the curves obtained after psychic excitement. The results in chart 5 should be compared with those in chart 2.

Again one notices a difference in the intensity and duration of the elevation of the blood pressure. The elevation may be as high as from 35 to 40 mm, as measured by the Riva-Rocci sphgmomanometer, and disappears later than it does in young persons. Moreover, the curves may become flat and plateau-like. These curves show, in addition, the deficient compensating power of the regulating mechanism. This can be regarded also as an initial sign of an inclination to hypertension in elderly persons.

In some cases I have observed that the labor test brought out a latent disturbance of the regulating mechanism, while the psychic reaction was of normal type. By means of these methods, it may be possible to separate various types of disturbances of the blood pressure, one of which may be due purely to psychic disorder.

CONCLUSIONS

The blood pressure in persons of presenile age is fluctuating and has a tendency to rise intensively after various irritations. The regulating mechanism of blood pressure is becoming insufficient. Hypertension after the performance of work or after psychic excitement is of a markedly longer duration in older than in younger persons, and diminution in the elevation of the blood pressure follows slowly. In this respect the behavior of elderly persons is similar to that of persons suffering from arterial hypertension.

The psychic test gives valuable evidence of the important rôle of psychic factors in the pathogenesis of arterial hypertension. The beginning incompetency of the regulating apparatus gives the basis for the eventual persistence of temporary elevations of blood pressure, which are otherwise rapidly compensated for by a well working regulating mechanism.

Usually, labor and psychic tests give the same results, but discrepancies sometimes occur.

THE VALUE OF THE DIAZO TEST ON BLOOD*

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This paper is a report of a study of the blood diazo test and of the conclusions deduced. Blotner and Fitz,¹ the first workers in this country, reviewed the papers of Andrewes² and Hewitt³ of England, of Becher⁴ of Germany and of Rabinowitch⁵ of Canada. Their work and the recent publication of the studies of Patch and Rabinowitch⁶ have been reviewed by us.

Andrewes,² while performing the van den Bergh test for bilirubin in the blood, noted a deviation from the normal color. He then added alkali to the end-product and obtained a pink coloration instead of the green of azobilirubin, this occurred only in persons with markedly damaged kidneys. He also found a blood bilirubin less than normal in amount in the same patients. Van den Bergh⁷ recognized a hypobilirubinemia in chronic nephritis. Beth,⁷ another German worker, differentiated malignant nephrosclerosis from chronic nephritis by the hyperbilirubinemia present in the former, as contrasted with the low level of bilirubin in the latter. Andrewes found the diazo test positive only in those persons having at least 220 mg of urea (103 mg urea nitrogen) per hundred cubic centimeters of blood. He waited twenty-four hours after blood was withdrawn before performing the test. This procedure, in our opinion, permitted the disintegration of the small amount of bilirubin present which might interfere with the test.

* From the Biochemical Laboratories of the Lebanon Hospital, New York.

1 Blotner, H., and Fitz, R. The Diazo Test in Nephritis, *J A M A* **88** 985 (March 26) 1927.

2 Andrewes, C. H. An Unexplained Diazo—Color Reaction in Uremic Sera, *Lancet* **1** 590 (March 22) 1924.

3 Hewitt, L. F. The Diazo Reaction in Uremic Sera, *Biochem J* **19** 171 (Feb) 1925.

4 Becher, E. Die Diazo und Urochromogenreaktion in Blutfiltrat bei Niereninsuffizienz, ihre Erklärung und klinische Bedeutung, *Deutsches Arch f klin Med* **148** 10 (July) 1925.

5 Rabinowitch, I. M. Observations on the Value of the Diazo-Color Reaction in the Differential Diagnosis of Uremia, *Canad M A J* **15** 725 (July) 1925.

6 Patch, F. S. and Rabinowitch, I. M. Urea and Creatinine Contents of the Blood in Renal Disease. A Statistical Analysis of Five Thousand Observations, *J A M A* **90** 1092 (April 7) 1928.

7 Quoted by Andrewes (footnote 2).

TABLE 1—*Casual Showing Positive Diazo Test*

Name	Sex*	Age	Clinical Diagnosis	Date	Urea Nitrogen	Non-protein Nitrogen	Creatinine	Phenol-sulphon-phthalein Test	Blood Pressure	Duration of Retention in Minutes	Comment
1 D R	♀	72	Hypertension, chronic nephritis pyonephrosis	5/17/27	103 72 43 43 43	115 85 62 62 63	6.3 3.3 3.8 2.9 3.1		120/80 130/70	12 2 2 2 0	Died of heart failure, no signs of uremia at any time
2 N S L	♂	11	Acute nephritis	7/21/27	49	83	4.0	<5%	172/114 136/90	2½ 1 1½	Died in uremia No signs of uremia at any time, now all edema, blood pressure 165, dizziness and spots before eyes
4 G R	♀	4	Paratuberculous nephritis, acute suppression of urine, uremia	8/22/27 8/23/27 8/24/27 8/25/27 8/26/27 8/27/27 8/28/27 8/29/27 8/30/27 9/1/27 9/2/27 9/3/27 9/4/27 9/5/27 9/6/27 9/7/27 9/8/27 9/9/27 9/10/27 9/11/27 9/12/27 9/13/27 9/14/27 9/15/27 9/16/27 9/17/27 9/18/27 9/19/27 9/20/27 9/21/27 9/22/27 9/23/27 9/24/27 9/25/27 9/26/27 9/27/27 9/28/27 9/29/27 9/30/27 10/1/27 10/2/27 10/3/27 10/4/27 10/5/27 10/6/27 10/7/27 10/8/27 10/9/27 10/10/27 10/11/27 10/12/27 10/13/27 10/14/27 10/15/27 10/16/27 10/17/27 10/18/27 10/19/27 10/20/27 10/21/27 10/22/27 10/23/27 10/24/27 10/25/27 10/26/27 10/27/27 10/28/27 10/29/27 10/30/27 11/1/27 11/2/27 11/3/27 11/4/27 11/5/27 11/6/27 11/7/27 11/8/27 11/9/27 11/10/27 11/11/27 11/12/27 11/13/27 11/14/27 11/15/27 11/16/27 11/17/27 11/18/27 11/19/27 11/20/27 11/21/27 11/22/27 11/23/27 11/24/27 11/25/27 11/26/27 11/27/27 11/28/27 11/29/27 11/30/27 12/1/27 12/2/27 12/3/27 12/4/27 12/5/27 12/6/27 12/7/27 12/8/27 12/9/27 12/10/27 12/11/27 12/12/27 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Hewitt³ improved Andrewes' technic in that he heated the reaction mixture instead of waiting twenty-four hours. The heat probably destroyed the bilirubin present. In his series of cases, the diazo test was positive when the urea averaged 366 mg (170 mg urea nitrogen) per hundred cubic centimeters of blood.

Finally, Rabinowitch⁵ added to the work by noting the accompanying creatinine. A positive diazo test was obtained in cases in which the urea nitrogen was as low as 71 mg and the creatinine 3.84 mg per hundred cubic centimeters of blood. He concluded that a positive reaction was

TABLE 2—Cases in Which There Appeared Clinical Signs of Uremia or High Blood Nitrogen Values or Both, with a Negative Diazo Test

Name	Sex*	Age	Clinical Diagnosis	Urea Nitrogen	Non-protein Nitrogen	Creatinine	Comment
1 S C	♂	65	Hypertrophy of prostate	72	108	6.0	Alive
				73	125	4.6	
2 S D	♂	71	Hypertrophy of prostate, acute uremia, bronchopneumonia	80	100	2.4	Died
3 I K	♂	43	Nephrolithiasis	43	85	6.7	Alive
4 M R	♂	69	Hypertension, chronic nephritis, acute uremia	51	68	3.3	Died
5 F L	♀	70	Acute nephritis, acute uremia	98	125	2.4	Died in coma
6 A I	♀	27	Lobar pneumonia	58	89	2.2	Alive
7 P T	♂	84	Ileus, acute uremia	66	97		Died in coma
8 I S	♂	20	Streptococcus hemolyticus septicemia	43	73	3.8	Died
9 M W	♂	61	Uremia cardiac decompensation	60	86	2.7	Died in coma
10 H S	♀	27	Bichloride poisoning	72	110	7.9	Died
11 A H	♀	57	Diabetes mellitus, chronic nephritis, uremia	140	170	4.6	Died in coma
12 R A	♀	9	Acute nephritis, acute uremia		40	1.8	Alive
13 F L	♀	55	Chronic nephritis, acute uremia	49	76	1.5	Died in coma
14 M K	♂	38	Bronchopneumonia, chronic nephritis, uremia	157	200	6.0	Died

* In this column, ♂ indicates male, ♀, female

seen in patients with definite uremia, and that it was not always associated with a fatal termination (one case). It was also thought that the test might be of greater prognostic significance in chronic nephritis than the determination of the blood creatinine values.

In a series of cases reported by Blotner and Fitz,¹ no case in which the urea nitrogen was below 28 mg per hundred cubic centimeter of blood showed a positive diazo test. They believed a positive reaction to be of grave significance, as twenty-eight of their thirty-six patients had died within one year. According to them, the test was valuable in the differentiation of uremic coma from coma of other origin.

In the present study, the diazo test was performed in the manner described by Hewitt, plasma being used chiefly. The test was performed

as a routine on 415 consecutive blood specimens collected in the wards of the Lebanon Hospital, and then in 40 more selected cases in which clinical observations or chemical examination of the blood indicated severe damage to the kidney

In all, seven patients gave a positive diazo reaction of the blood. Of these, four are now living, and their general condition has improved. The positive reaction seemed to follow the level of creatinine rather than that of the other nitrogenous components of the blood. Contrary to the observations of some of the other workers,⁶ a positive reaction was obtained in specimens having a creatinine value as low as 1.8 mg per hundred cubic centimeters of blood. Unlike these workers we have found the test negative on samples of blood containing more than 3 mg of creatinine per hundred cubic centimeters of blood. The highest creatinine figure with a negative diazo test was 7.9 mg per hundred cubic centimeters.

A study of table 2 warrants the statement that the diazo test is not always positive in cases in which there are clinical and laboratory signs of uremia. This holds true even of patients in uremic coma, and does not support the view that the positive diazo test is a means of differentiating uremic coma from coma of other origin.¹

The claim has been advanced that the diazo test is not positive in cases of nitrogen retention due to obstruction of the kidney. In case 7 in table 1 (patient J. C.), there was a positive reaction which became negative on relief of the obstruction, even though the nitrogen values remained high.

SUMMARY

1. Seven cases showed a positive diazo test. Four of these patients are now living and their general condition has improved.

2. The diazo test is not positive in all cases showing coma or other evidence of a severely damaged kidney.

3. The positive diazo test does not always differentiate uremic coma from coma of other origin.

4. No definite creatinine value can be established as the point at which the positive diazo reaction appears.

5. The determination of the amount of creatinine present is of greater value than is the diazo test in estimating the extent of damage to the kidney.

6. The diazo test may be positive in cases in which there is obstruction of the kidney.

7. If the diazo test is to be performed it should be done as a routine regardless of clinical signs or blood nitrogen values on the blood of patients whose kidneys are believed to be damaged.

FUNCTIONAL INSUFFICIENCY OF THE SUPRARENAL GLANDS *

C A MILLS, M D

PEKING, CHINA

Since the description by Addison, in 1855, of the disease that bears his name, many articles have been written on dysfunction of the suprarenal glands, and many cases have been reported that have shown the picture of insufficiency of these glands as described by him. Most of the autopsies reported have shown destruction of the suprarenal tissue by tuberculosis, tumor, hemorrhage, acute infection, thrombosis or some other direct-acting agency. Investigators have also described an enlargement, loss of pigment and disappearance of the medulla of the gland in wasting diseases, particularly in diseases due to inanition and dietary deficiencies (vitamins). It is not necessary to review the mass of literature in detail, since it is summarized in the articles here cited ¹

The purpose in this article is to point out a type of suprarenal insufficiency frequently seen in certain regions, which seems to be associated with definite climatic factors, and which responds well to the administration of epinephrine orally. I wish also to point out the close similarity of the symptoms and observations in several of these cases to those in peptic ulcer, chronic appendicitis and tuberculous enteritis and to emphasize the importance of considering dysfunction of the suprarenal glands in the differential diagnosis of such disturbances of the gastro-intestinal tract.

Natives of the cooler portions of the temperate zone who take up residence in the tropics frequently become subject to disturbances of the gastro-intestinal tract and to a general loss of vitality and vigor which seriously impair their usefulness and necessitate frequent and expensive home leaves for recuperation. These disturbances often occur during the first year of residence in the tropics, but they may not appear for several years. The principal gastro-intestinal symptoms are a tendency to diarrhea (in most cases without the presence of pathogenic organisms in the stools), achlorhydria or hypochlorhydria with impaired digestion and hypermotility of the whole tract. Spasticity of the cardiac, pyloric or ileocecal sphincter is often present. These disturbances are usually

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¹ Reisman, David. Oxford Medicine, London, Oxford University Press, 1921, vol 3 p 783. McCarrison, Robert. Studies in Deficiency Disease, London Oxford University Press, 1921. Biedl, Arthur. Internal Secretory Organs, New York, William Wood & Co 1913.

accompanied by a fall in blood pressure, anemia, loss in weight and progressive weakness and lassitude. Tropical sprue is probably only an exaggeration of this condition. Vascular hypotension and lowered basal metabolism have been observed in many tropical and subtropical countries, but so far no one has found an explanation for the condition. Dietary differences have been suggested as the cause of these changes but foreigners in the tropics eat much the same kinds of food as they do in their home lands. In New Orleans it was found that, although the basal metabolic rate is subnormal, the average caloric intake is about the same as in cooler latitudes.²

Northern China, Korea and Japan are far removed from the tropics, and yet the same body disturbances as occur in foreigners in the tropics are met with here to an almost equal extent. The native people of Northern China also show the same subnormal metabolism and hypotension as are seen in both foreigners and natives living in the tropics. Tung³ has shown that Americans coming to Peking and Chinese students returning after several years in America, all exhibit a definite drop in both systolic and diastolic blood pressure after a few years of residence in this country. This observation of tropical effects so far north has led to much speculation concerning the cause. The mean yearly temperature in China is practically the same as that of similar latitudes in the United States, where few such disturbances are seen. The most striking resemblance of this climate to that of the tropics is the occurrence of the rainy season during the period of most intense summer heat. At one time in July, 1927, the temperature was 114 F in the shade, with a relative humidity of 92 per cent.¹

The accompanying charts showing the mean monthly temperature and relative humidity in Peking for several years were prepared by Dr. H. Necheles from data published in the *Peking Union Medical College Weekly Bulletin*. The third chart, showing the average monthly rainfall in Peking and Shanghai from 1900 to 1917, was prepared by Dr. A. M. Dunlap and published in the aforementioned bulletin, May 6, 1924. From these three charts, it is seen that June and July are the two warmest months and that the relative humidity and rainfall show sharp maxima coinciding with the maximum heat. During this period of intense heat and high humidity, the heavy rainfall affords little relief from the oppression. There is also little difference in the day and night temperatures, so that cooling of the body remains difficult at all times for a period of about six weeks. This same type of rainy season during the summer is met with throughout Northern China, Korea and Japan.

² Borgstrom, P. *Am J Physiol* **79** 221, 229, 237, 242 and 245, 1926.

³ Tung, C. L. *Relative Hypertension of Foreigners in China*, *Arch Int Med* **40** 153 (Aug) 1927, *Chinese J Physiol*, 1928, vol. 2.

I believe this yearly period of simultaneous high heat and high humidity to be the factor responsible for the disturbances of body function seen in the tropics and in those other regions having the rainy season during midsummer. In a surprising number of instances, the first history of body disturbance dates from this season, often from the first period of this kind encountered by the patient if he is a foreigner.

I am, of course, excluding from consideration those parasitic and bacterial diseases so frequent in the tropics. That they may be eradicated by proper hygienic precautions was strikingly illustrated in the Panama Canal Zone by Gorgas. It is recognized by many who are familiar with tropical conditions that, even with all such parasitic diseases excluded, there still will exist functional disability of such

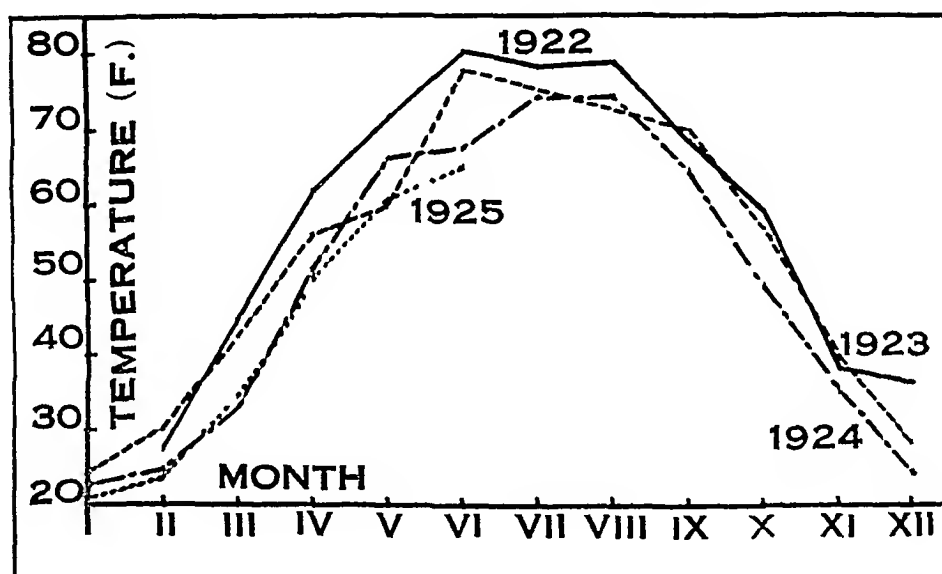


Chart 1—Chart showing the mean monthly temperature in Peking from 1922 to 1925

frequency and severity as seriously to impair the efficiency of workers there. It is this disturbance that I believe is caused by the hot, humid season when cooling of the body becomes extremely difficult.

The level of the production of heat under basal conditions seems definitely associated with the function of the thyroid gland, but above this level, the suprarenal glands appear to be responsible for the stimulation of the production of heat. It has been demonstrated⁴ that secretion of epinephrine increases in animals as the bodily activity or loss of heat is increased, while Boothby and Sandiford⁵ showed that the injection of epinephrine caused a marked increase in the production of heat.

⁴ Cannon, W. B. *Am J Physiol* **79** 466, 1926. Hartman, F. A., and Hartman, W. B. *Ibid* **65** 612, 1923.

⁵ Boothby, Walter M., and Sandiford, Irene. *Am J Physiol* **66** 93, 1923.

Sundstroem⁶ has shown that rats produce considerably less heat when kept in hot, moist air than under ordinary conditions, and that this depression is greatest when the air is not in motion. Cramer⁷ found marked changes in the suprarenals in mice kept in a temperature of from 37 to 38 C for several days, the principal change being a loss of the characteristic lipid from the cortex, which he interpreted as evidence of inhibition of function. It seems, therefore, that the difficulty of keeping cool in the hot humid season, wherever it occurs with sufficient intensity, serves to cause a marked suppression of suprarenal function, with the result that diarrhea and other disturbances of the gastro-intestinal tract appear on slight provocation. From the histories of the cases

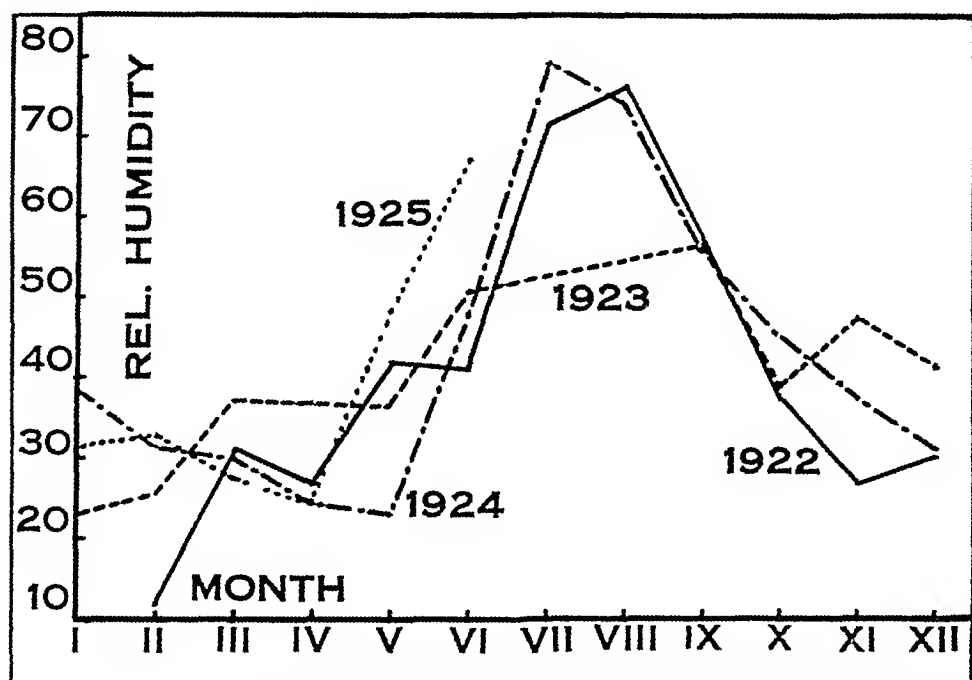


Chart 2—Chart showing the monthly mean of the relative humidity in Peking from 1922 to 1925

herein reported it would seem that this suprarenal depression is often so severe that function is not regained spontaneously, but may be brought about through a course of epinephrine therapy.

During the four months that have elapsed since I began this study, about forty cases of apparent suprarenal insufficiency have been encountered. A few of these were lost track of before definite results could be obtained. At present the number of such cases seen each week is rapidly increasing as various manifestations become more familiar. As time passes, the impression grows stronger and stronger that this condition

⁶ Sundstroem, E. S. *J. Biol. Chem.* **63** 41 (proceedings) 1925, *Physiol. Rev.* **7** 320, 1927.

⁷ Cramer, W. *Brit. J. Exper. Path.* **7** 88 and 95, 1926.

is probably responsible for a great amount of the ill health in regions in which the maxima of heat and moisture coincide. Nor is it a disease peculiar to foreigners in these regions, since many of my patients are Chinese. Interestingly enough, all my patients have been adults, which agrees with the observations of Sundstroom that the depressing effect of moist heat (on rats) was evident only in adult life. Aballi,⁸ however, has described two cases in patients 2 days and 5 months old, respectively, which occurred in Cuba.

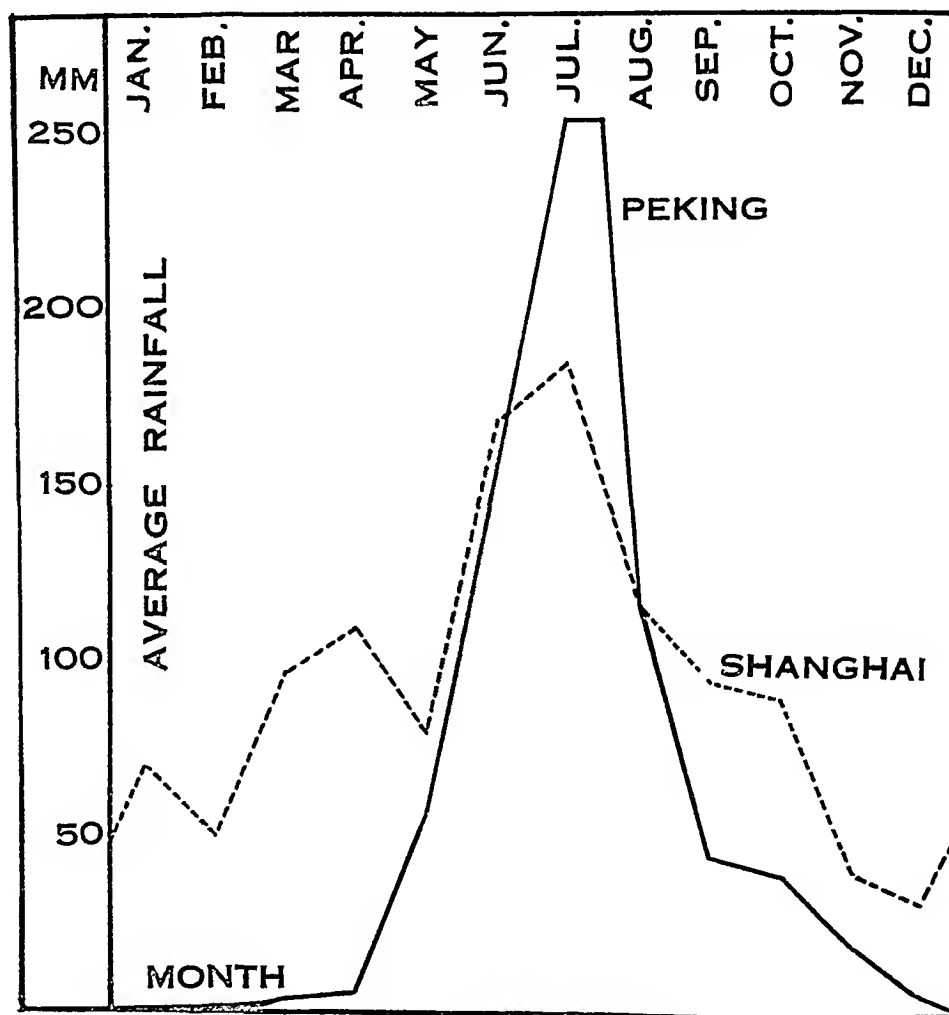


Chart 3—Chart showing the average monthly rainfall in Peking and Shanghai from 1900 to 1917

I have not had an opportunity to determine how many infants and children with summer gastro-intestinal disturbances, seen in all countries would be benefited by epinephrine therapy.

I shall present the histories of a few of the more typical cases in some detail, and briefly summarize the remainder in order to conserve space.

REPORT OF CASES

CASE 1 (Hosp no 18864)—*History*—A Chinese woman, aged 25, married, was admitted to the hospital on Dec 31, 1927. In January, 1927, her first and only pregnancy terminated in normal labor. The child was breast fed, the mother was strong and healthy. In June, she began to feel ill, complaining of a hot sensation in the chest and a dull aching in both lumbar regions. In August, she began to notice swelling of the feet, which gradually included the legs, abdomen and finally the face (in October). Fever and chilliness were present for the first two weeks, and the output of urine was markedly diminished. The movement of the bowels was irregular, sometimes there were four or five watery movements a day and again only one movement in from two to three days. In August, the child died of "cholera"—severe diarrhea. The patient's condition grew worse until October, when there was edema of the whole body, marked loss of appetite, general malaise and weakness. After October the swelling gradually subsided, but epigastric discomfort, vomiting and irregularity of bowel movements became worse. Two weeks before admission to the hospital, she again became feverish and noticed dyspnea and palpitation of the heart.

The past history was irrelevant except regarding menstruation. This began at the age of 17, the period being forty \pm days apart and accompanied by considerable pelvic pain. The patient had not menstruated since childbirth in January, 1927.

Physical Examination—The principal points shown by the examination were marked emaciation, dry, loose and scaly skin, edema of the feet and legs, abdomen somewhat doughy to palpation, lungs and heart normal and a blood pressure of systolic 76 and diastolic 50. The urine contained a trace of albumin but no casts. The phthalein output was normal. The blood showed moderate anemia (3,300,000 erythrocytes and 70 per cent hemoglobin). X-ray and fluoroscopic examination of the chest and gastro-intestinal tract did not show any abnormalities. Gastric analysis with an Ewald test meal demonstrated achlorhydria both before and after the intake of food and freedom from lactic acid. A dextrose tolerance test, using 100 Gm of dextrose orally, gave the following readings for the blood sugar: fasting, 95.5 mg per hundred cubic centimeters; half an hour after the administration of dextrose, 125 mg; one and a half hours after, 111 mg; and three hours after, 100 mg. The stools did not contain parasites or ova. The Wassermann test of the blood, the Widal and the Weil-Felix tests were negative. The basal metabolic rate was minus 9 per cent (Tissot apparatus).

Treatment and Course—During the first ten days in the hospital, the patient lost 6 pounds (2.7 Kg) in weight, and appeared to have a grave prognosis. She was extremely weak, with poor appetite, and had a continuous dull pain in the loins. The edema disappeared during this time, which probably accounts for much of the loss in weight. She was then given 1 mg of epinephrine orally before each meal. The pain in the lumbar region ceased within a day, the appetite improved and the patient gained 9 pounds (4.1 Kg) during the next week. The administration of epinephrine was then discontinued for the purpose of study, the pain in the lumbar region recurred for one day, and the patient lost 3 pounds (1.4 Kg) during the succeeding three days. During the next three weeks, when she was not given any medication, she slowly gained 2 pounds (0.9 Kg) and felt fairly well. Epinephrine was then again given, 1 mg daily before breakfast, and she gained 4 pounds (1.8 Kg) during the succeeding week. The patient is still under observation. The blood pressure has risen from 76 systolic and 50 diastolic to 94 systolic and 68 diastolic.

I present this case in detail because it is so clearcut and striking. The history of asthenia, emaciation, and pain in the lumbar region, the disturbances of the gastro-intestinal tract, achlorhydria, vascular hypotension, high degree of dextrose tolerance and the marked response to epinephrine combine to give a clearcut picture of suprarenal insufficiency. Tuberculous enteritis or peritonitis was suspected on admission but supporting evidence was not obtained.

CASE 2 (Hosp no 18,922) —*History*—A Chinese man, a student, aged 24, was admitted to the hospital on Dec 19, 1927, complaining of diarrhea since May, 1927, with great weakness and loss in weight. He came as a student from Shansi to Peking three years previous to the time of admission. Each summer during his stay in Peking he had had severe diarrhea, with bloody and mucous stools. The blood and mucus disappeared each time after about ten days, but since the attack in May, the bowel movements had continued from three to four times a day, they were watery, but were not accompanied by pain. He had had occasional attacks of nausea without vomiting. Ten days before admission, he began to cough and expectorate a whitish sputum. There was no fever. The appetite was entirely gone, and the patient was too weak to stand alone.

Physical Examination—Marked pallor and emaciation, with pitting edema of the feet, were present. The abdomen was full, tense and doughy. The lungs and heart were normal. The blood pressure was 92 systolic and 50 diastolic. The urine showed a faint trace of albumin. There were 3,000,000 red cells with 50 per cent hemoglobin. The number of white blood cells was normal. X-ray examination showed that the chest was normal. X-ray and fluoroscopic examination of the gastro-intestinal tract showed retention in the stomach and retention and dilatation in the ileum suggesting adhesive peritonitis (tuberculous?). The results of examinations of the stool, the Wassermann, Widal and Weil-Felix tests were all negative. The clinical impression was that the patient had tuberculous enteritis or peritonitis or both.

The course of the patient was rapidly downhill, he had fever, dehydration and diarrhea. He died on the sixth day after admission.

Autopsy—Autopsy, performed by Dr J R Cash, showed some evidence of bronchopneumonia of recent date and marked atrophy of the viscera, especially of the heart and liver, but the suprarenal glands were slightly enlarged and softer than normal. On section, the cortex appeared pale, yellowish gray and was somewhat translucent. Near the edges of the suprarenals, the medulla was represented by a thin brown line to which the opposing layers of cortex were adherent. In the central portion of the glands, the medulla had become softened in large areas. Sections made midway between the center and the poles of the glands revealed the medulla to be thick, pale gray and showing a thin line of softening next to the cortex. There was no evidence of tuberculosis anywhere in the body. The peritoneum was normal, as was also the gastro-intestinal tract, except for atrophy. No local cause could be found for the diarrhea.

The principal value of this case is in the report on the autopsy. The clinical and x-ray impressions were that tuberculous enteritis or peritonitis was the cause of death, although on looking back, the similarity to semiacute suprarenal insufficiency can be seen. The patient was not seen by me. The lack of any pathologic changes to account for the

patient's condition, other than those in the suprarenal glands, seems to justify the diagnosis of suprarenal insufficiency with a terminal bronchopneumonia

CASE 3 (Hosp no 19,133) —History—A Chinese girl, aged 15, was admitted to the hospital on Jan 12, 1928, complaining of irregularity of menstruation, with profuse and prolonged bleeding. Menstruation began in March, 1925. There were four periods in 1926 and one in May, 1927. The last one began about December 15 and was still continuing at the time of admission. Except for the last period, the duration was about a week, with profuse bleeding but without pelvic or abdominal pain.

About two months before admission, the patient noticed some pallor. Since December 15, she had been weak and for the last ten days had been troubled with dizziness and loss of appetite and weight. There was no history of other bleeding or ailments, except constipation for several months previously. She came from Hunan to Peking in 1925.

Physical Examination—Rather marked pallor, slight emaciation, a soft blowing systolic murmur heard over the whole heart, and a blood pressure of 94 systolic and 60 diastolic were present. The red blood cells numbered 2,340,000 with 35 per cent hemoglobin. The white cell count was normal. Urinalyses revealed a normal urine. X-ray examination of the chest showed the lungs clear and the heart 15 sq cm undersize.

Treatment and Course—On the basis of the menstrual history, hypotension and constipation, with negative physical observations, the diagnosis of suprarenal insufficiency was made, and epinephrine was given orally. On January 16, the patient received 1 mg before each meal, which resulted in a marked lessening of the bleeding on that day and on the succeeding one. On January 18, she began to receive 1 mg daily before breakfast. On the next day, the bleeding completely ceased and did not recur during the patient's stay in the hospital. On January 20, the red cell count had risen to 3,710,000, with 45 per cent hemoglobin. The patient was discharged on January 22, to be followed in the outpatient department.

CASE 4 (Hosp no 18,585) —History—A Chinese man, aged 37, was admitted to the hospital on Nov 12, 1927, complaining of epigastric pain for the past year. One year previous to the time of admission, he attended a banquet and drank a great deal of wine. An hour and a half later he became nauseated, had epigastric and abdominal pain, and noticed profuse sweating and trembling. The next morning a tarry stool was passed, and pallor of the face and lips was present. In two days, he became better, but he has since suffered from a dull pain in the right hypochondrium. In September, this pain grew worse, culminating in another severe attack on November 7. There were three spasms of pain during the day, each lasting from five to fifteen minutes. He became nauseated but did not vomit. The stools of the next three days were tarry.

Physical Examination—The results of the examination were normal, except for moderate obesity and the presence of small hemorrhoids. The blood pressure was 102 systolic and 74 diastolic. Gastric analysis before and after an Ewald test meal showed free acid of 58 and 79. Examination of the blood, urine and stool gave normal observations. X-ray examination of the gastro-intestinal tract did not show any abnormality, except some stasis in the lower part of the ileum.

Treatment and Course—A tentative diagnosis of duodenal ulcer was made by the attending physician but with the idea that the condition might be purely a

functional disturbance, the administration of epinephrine, 1 mg twice daily, was begun on November 19. Up to this time the patient had been having a great deal of abdominal pain and was constipated. Within two days after the administration of epinephrine was begun, the pain ceased, and the bowel movements were normal. The epinephrine therapy was discontinued November 28, and when last seen December 16, the patient was still free from pain and was having normal bowel movements.

The clinical diagnosis of duodenal ulcer was plausible in this case, but as complete relief was obtained by the use of epinephrine, the condition must be considered functional rather than organic. Acute spasm of the pylorus must have occurred at the time of the attacks, causing congestion of the mucosa and hemorrhage.

CASE 5 (Hosp no 19,162) —History—A Russian, aged 26, was admitted to the hospital for study on Jan 14, 1928, complaining of obstinate constipation since October, 1924. He came to China from Siberia in 1923, and the next fall (October 1924) began to be constipated, although otherwise well. The use of cathartics caused a great deal of pain in the right lower quadrant of the abdomen. He complained of slight abdominal pain early each morning. The results of physical and x-ray examinations were negative, except that some tenderness of the sigmoid colon was noted. The blood pressure was 106 systolic and 66 diastolic. The blood, urine and stools were normal. A dextrose tolerance test, using 100 Gm of dextrose, gave 95.5, 153.8, 133.3 and 80 mg per hundred cubic centimeters of dextrose, respectively, in samples of blood taken during fasting, and half an hour, one and a half hours and three hours later.

Treatment and Course—The oral administration of 1 mg of epinephrine daily was begun on January 17, and spontaneous bowel movements started the next day. The patient suffered from acute gastric distress ten minutes after taking the first dose of epinephrine, so the dosage was reduced to 0.6 mg daily. Word was received from him on February 28 saying that he was normal in all respects, and that he had been without epinephrine for a period of three weeks.

The diagnosis in this case was spastic constipation, beginning shortly after the patient's first summer in China, and showing prompt relief following the use of epinephrine.

CASE 6 (Hosp no 878) —History—A Swiss man, aged 39, was first seen by me on Sept 22, 1927. He had been in poor condition for ten years, suffering from constipation, loss of weight, nervousness, indigestion and general lack of proper vitality. Abdominal and epigastric pain readily followed indiscretions in food. Physical examination did not show any abnormality, except the presence of hemorrhoids. All the various laboratory procedures gave normal results.

Treatment and Course—On Sept 22, 1927, the patient began to take 1 cc of epinephrine (1:1000) sublingually each day, with the following results. On September 22, the weight was 67.3 Kg (148 pounds) and the blood pressure was 115 systolic and 70 diastolic. On September 30, he weighed 68.3 Kg (151 pounds), and the blood pressure was 100 systolic and 62 diastolic. On October 24, the weight was 70.9 Kg (156 pounds), and on December 6 he weighed 72 Kg (159 pounds). The blood pressure was then 130 systolic and 80 diastolic, the patient felt well and was full of vitality. The bowel movements had been regular and normal since the onset of epinephrine therapy. On February 11, he was again seen, at which time he weighed 73 Kg.

(161 pounds) and had a blood pressure of 124 systolic and 84 diastolic. After the last preceding visit, December 6, the dosage of epinephrine was reduced gradually to 4 drops daily, and finally on January 18 it was stopped completely. Within three days, the patient began to be constipated and to have a feeling of weakness and collapse. He took 8 drops of epinephrine solution on January 22, and within a day was again feeling normal. This daily dose was again gradually reduced and withdrawn on February 2. Up to the time of this visit, he had felt normal for nine days. The advice given to him is that he abstain from the epinephrine, using it only temporarily in case of need.

The gain of 12 pounds (5.4 Kg) in the weight of this patient and the general improvement under epinephrine therapy were marked. Of special interest is the steady rise in the diastolic blood pressure to a normal level.

CASE 7 (Hosp. no. 17,923)—*History*—An American man, aged 46, was admitted to the hospital on Sept. 4, 1927, complaining of severe epigastric and abdominal pain, constipation, weakness and loss in weight. He came to China in April, 1927, landing at Shanghai, where he had had severe diarrhea for a period of four days, without blood or mucous in the stools, but with severe pain. In June, he came to Peking and at once had a similar attack (fifteen bowel movements a day). On August 16, he had still another attack, which was acute and was accompanied by vomiting and severe gastric pain. The diarrhea lasted only one day, after which constipation occurred, but the pain in the stomach persisted. On admission, he complained of substernal pain and a choking feeling after swallowing, of pain in the stomach which was present at all times but which was worse after meals, and of pain in the lower part of the abdomen accompanied by much gurgling. He gave a history of a similar attack of diarrhea with vomiting and gastric pain in 1907 during a visit in Japan. This attack had ceased spontaneously a few weeks after leaving Japan. In 1923, ulcer of the stomach had been diagnosed in America because of the presence of gastric pain and pylorospasm.

Physical Examination—Results of examination revealed little except that the patient was an intensely nervous and thin person, with a blood pressure of 124 systolic and 76 diastolic. X-ray examination of the chest did not show any abnormality, that of the gastro-intestinal tract showed only marked hyperperistalsis of the stomach. Visualization of the gallbladder by the Graham test was normal. Observations on the blood and urine were normal, except for the presence of a low amount of sugar in the blood during fasting, 66.6 mg. per hundred cubic centimeters. All examinations of the stool gave normal results. The blood pressure showed a tendency to marked decline during the late afternoon if the patient exerted himself much, and at such times severe occipital headache began.

Treatment and Course—The diagnosis of suprarenal insufficiency, with hypermotility of the gastro-intestinal tract and spasticity of the sphincters was made, and 1 mg. of epinephrine was given sublingually before breakfast each day, beginning on September 8. Within three days the painful peristalsis of the lower part of the abdomen had ceased, and after another two days the cardiospasm and epigastric discomfort were entirely relieved, and the bowels were functioning normally. After eight days of epinephrine therapy, the patient left the hospital and stopped the use of epinephrine. Two weeks later, he returned with the former symptoms and again was completely relieved by the administration of epinephrine. This time he took the drug for three or four weeks. Six weeks later, Oct. 19,

1927, he reported a gain in weight of 20 pounds (9 Kg) and perfect function of the gastro-intestinal tract without epinephrine therapy. He said that he felt better in general than he had ever felt before in his adult life. He reported similarly in January, 1928.

This case presents the typical picture of suprarenal insufficiency with hypermotility of the entire gastro-intestinal tract and spasticity of the sphincters, and also a tendency to vascular hypotension on exertion instead of the relative hypertension which effort should call forth. The low amount of blood sugar and alternating diarrhea and constipation completed the picture. The relation of the onset of this trouble to the patient's arrival in the Orient is definite. The latter part of April in Shanghai is warm and moist. His worst attack in Peking occurred just at the end of the period of high temperature and humidity.

CASE 8 (Hosp. no. 13,768)—*History*—An American woman, aged 36, came to China by way of Japan in July, 1927, having been in good health in America. As she approached Japan, hot, humid weather was encountered, and she developed a moderate but continuous diarrhea and edema of the feet and ankles. When she arrived in Peking in July, both the edema and diarrhea grew markedly worse. There was some mucus but no blood in the stools. Pathologic organisms were not found then or subsequently. She felt tired and weak, and complained of cramplike pains in the abdomen. There was some dull epigastric pain and distention, and constant gurgling in the intestines. There was no fever. Physical examination then or later did not reveal any abnormalities. In August, 1924, she had had an attack of giant urticaria following bathing and exposure to the sunlight.

The edema disappeared in the course of two months, the diarrhea improved to from three to four stools daily, and she felt rather normal. Every few weeks exacerbations would occur, especially at the menstrual periods. Another severe attack occurred in September, 1925, after a fatiguing trip into Mongolia during the hot weather.

The family history is interesting in that the father suffers from asthma, and the mother from angioneurotic edema, while the mother's father died of Addison's disease.

On March 11, 1925, gastric analysis revealed achlorhydria, the blood counts were normal and the blood pressure was 112 systolic and 70 diastolic. On May 11, 1926, the number of red cells had decreased from 5,200,000 to 4,550,000, and the blood pressure from 112 systolic and 70 diastolic to 94 systolic and 60 diastolic. There was still complete achlorhydria. The sigmoid colon was easily palpable and thickened. There was marked peristalsis in the lower part of the abdomen. X-ray examination of the chest and gastro-intestinal tract was negative. The blood sugar during fasting at this time was 90 mg per hundred cubic centimeters. On April 2, 1927, the red cell count had fallen to 4,000,000 per cubic millimeter.

Treatment and Course—In July, 1927, she had another severe attack of diarrhea with frothy watery stools. She vomited once during this attack. While the attack continued, she was given 0.3 cc of epinephrine (1:1,000) subcutaneously once a day for five days, and then 0.5 cc a day sublingually for two weeks. The improvement was immediate and definite, the stools becoming fewer, and the patient feeling much better while the epinephrine was given and for several months thereafter.

In this case, the direct relationship between the onset of trouble and contact with tropical summer weather is again evident. The hyperperistalsis, diarrhea, epigastric discomfort, decrease in blood pressure edema, achlorhydria and urticarial reaction all point to an insufficiency of the suprarenal glands brought on by the tropical heat.

CASE 9 (Hosp. no. 19,023)—History—A Chinese man, aged 60, was admitted to the hospital on Dec. 30, 1927, complaining of inability to eat solid food for the previous six months. In December, 1926, he had begun to notice some difficulty in swallowing solid food. This had gradually become worse until July, since which time nothing solid had been taken. There had been occasional regurgitation of food before July, and frequently during the last six months. The material regurgitated was always in the same form as when eaten. There was a sense of pressure under the sternum after eating, but no actual pain. There was never blood in the vomitus or stools. The appetite remained good, although there was marked loss in weight because of the limited intake of food. The patient was constipated throughout this period.

Physical Examination—Examination revealed marked emaciation, arteriosclerosis, a blood pressure of 100 systolic and 70 diastolic, and a moderately enlarged spleen. The observations on the blood and urine were normal. A few entameba cysts and *Ascaris* eggs were found in the stools. The Wassermann test of the blood was negative. X-ray and fluoroscopic examinations showed delay of the barium at the cardia with dilatation and antiperistalsis. There was no filling defect. The cardia was seen to open and discharge barium from six to eight seconds after the patient swallowed, showing that opening was possible. Esophagoscopy did not reveal any pathologic change or new growth, only spasm of the sphincter.

Treatment and Course—On the basis of the negative observations for organic lesion, and in view of the vascular hypotension and constipation, the patient was given 1 mg. of epinephrine orally before each meal, beginning on January 4. He was put on a full diet on January 7, and did not experience further difficulty in swallowing. The bowel movements became regular and normal two days after the medication was started.

In the table are summarized the principal features of all the cases so far studied, including those presented in detail in the preceding pages. Certain points are apparent in a study of this series of cases:

1. The disturbance affects foreigners in China much more than it does the Chinese. Foreigners constitute almost half in this series, but in this hospital the total number of admissions of foreign and Chinese patients for 1927 was in the ratio of 1:5, so that foreigners must be much more susceptible to this disturbance than are the Chinese.

2. Among the eighteen foreigners studied, the disturbance began in six of them less than one year after their coming to China. In some of these, the relation of onset to arrival in China was so definite that there could be little doubt that the climatic change was responsible.

3. The time of onset of symptoms, when this could be definitely established, was during the summer or fall.

Tabulation of Cases of Suprarenal Insufficiency

Hosp No	Nationality	Sex	Age, Years	Time in China Before Onset	Month of Onset	Principal Disturbances	Blood Pressure	Result of Treatment With Epinephrine
18864	Chinese	F	25	Since birth	June	Diarrhea, edema, emaciation, achlorhydria	76/50	Relief at once
18922	Chinese	M	24	Since birth	May	Diarrhea, edema, weakness, emaciation	92/50	No treatment, died
19133	Chinese	F	15	Since birth	Dec	Menorrhagia, anemia	94/60	Relief at once
18585	Chinese	M	37	Since birth	Nov	Epigastric pain, constipation, intestinal bleeding	102/70	Relief at once
19162	Russian	M	26	1 year	Oct	Constipation abdominal pain	106/66	Relief at once
878	Swiss	M	39	5 years	Indefinite	Constipation, weakness, abdominal pain	100/62	Relief in a few days
17923	American	M	46	Few weeks	April	Diarrhea, constipation, cardiospasm, pylorospasm, emaciation, weakness	124/76	Relief in a few days
13768	American	F	36	On arrival	July	Diarrhea, edema, urticaria, weakness, achlorhydria	94/60	Some improvement at once
19023	Chinese	M	60	Since birth	Dec	Cardiospasm, emaciation, constipation	100/70	Relief at once
19080	Chinese	M	27	Since birth	July	Diarrhea, weakness, constipation, abdominal pain, vomiting, edema	104/64	Relief with rest in bed
19228	American	F	34	1 year	Summer	Constipation, weakness, pain in epigastrium, hypochlorhydria	98/64	Good effect in few days
19120	Chinese	M	25	Since birth	July	Diarrhea, abdominal pain, loss in weight	98/58	No report
19125	Chinese	M	50	Since birth	Dec	Pylorospasm, constipation, loss in weight, anemia, achlorhydria	120/40	No treatment
18732	American	F	34	5 years	June	Diarrhea and constipation, visceroptosis, hyperstalsis, abdominal distention	100/60	Prompt relief
19167	American	F	36	4 years	May	Diarrhea, headache and fainting	93/58	No report
4986	Russian	M	40	Before coming		Heartburn, epigastric distress, weakness, constipation, hemorrhoids, pylorospasm	100/60	No report
3073	Chinese	F	24	Since birth	Indefinite	Dysmenorrhea, menorrhagia, diarrhea and constipation, epigastric discomfort, vomiting, anemia	100/70	Prompt relief
18753	American	F	38		Indefinite	Pain in right iliac fossa, dysmenorrhea, neuroasthenia	98/60	Prompt relief
19707	Chinese	M	34	Since birth	August	Abdominal pain and distention vomiting, diarrhea and constipation, fever and loss in weight	92/54	Prompt improvement
16571	Chinese	M	22	Since birth	Indefinite	Constipation, loss in weight	90/58	Prompt relief
16262	Chinese	F	27	Since birth	Indefinite	Abdominal pain, nausea, vomiting, diarrhea, dysmenorrhea, epigastric pain, headache, fainting	84/56	No effect
13504	American	F	36	9 years	Fall	Nausea, dizziness, headache, dysmenorrhea, constipation	80/50	No report
19602	Chinese	F	49	Since birth	Dec	Fever, malaise, tetany, epigastric distress, vomiting, emaciation, achlorhydria	70/50	Good effect
19170	Chinese	M	20	Since birth	July	Diarrhea, abdominal pain, loss in weight	86/44	No report

Tabulation of Cases of Suprarenal Insufficiency—Continued

Hosp No	Nationality	Sex	Age, Years	Time in China Before Onset	Month of Onset	Principal Disturbances	Blood Pressure	Result of Treatment With Epinephrine
15905	American	F	28	2 months	Dec	Diarrhea, constipation, epigastric pain	95/65	Good effect
	Chinese	M	50	Onset in U S A	Summer	Asthma for 23 years' standing	96/66	No effect
17068	American	M	54			Diarrhea, abdominal pain, loss in weight, anemia, achlorhydria	94/66	Good effect
18948	Chinese	M	37	Since birth	Aug	Pylorospasm, vomiting, emaciation, constipation, hypochlorhydria	82/64	No report
16462	Chinese	M	21	Since birth	Sept	Constipation, abdominal pain, pylorospasm	108/62	Relief at once
18694	Swedish	M	31	5 years	Sept	Abdominal pain, nausea, constipation, hypochlorhydria	96/62	Relief in a few days
17675	Chinese	M	46	Since birth	Aug	Severe dysentery, diarrhea persisted for weeks after infection was gone		Cessation of diarrhea at once
18297	Chinese	M	66	Since birth	May	Cardiospasm, heart failure, arteriosclerosis	104/58	Doubtful
17233	American	M	41	4 years	Indefinite	Dull abdominal pain, hyperperistalsis, some constipation, hypochlorhydria	115/72	Prompt relief
18902	Chinese	M	25	Since birth	Summer	Vomiting, weakness, pylorospasm, constipation	110/74	No report
15930	American	F	37	10 years	Indefinite	Epigastric distress, hives, urticaria, pigmented areas of skin	88/56	No report
19285	American	M	35	8 years	June	Indigestion, diarrhea, loss in weight and strength, constipation	100/50	No report
19532	Chinese	F	30	Since birth	Indefinite	Epigastric pain, vomiting, pain in right iliac fossa, constipation	78/50	Prompt relief
8204	American	M	34	11½ years	June	Diarrhea, discomfort in left upper quadrant	80/40	Prompt relief
19817	Chinese	M	32	Since birth	May	Epigastric pain, constipation, undernourishment intestinal obstruction	74/50	
19803	Russian	F	45	2 months		Epigastric pain, constipation, nausea, vomiting, emaciation, cough, weakness, amenorrhea, achlorhydria	90/50	Prompt relief of symptoms and gain in weight

4 Both sexes are about equally afflicted

5 The principal symptoms complained of are diarrhea or constipation or both alternating, abdominal and epigastric pain, nausea and some vomiting, weakness and loss of weight, pylorospasm, cardiospasm and anemia. There also occurred urticaria, pigmentation of the skin, edema, menorrhagia and marked vascular hypotension. Both systolic and diastolic blood pressures are, in general, even considerably below the low values so commonly found in China. The blood pressure of the foreigners of this series shows much greater deviations from the normal than does that of the Chinese.

6 In some of the cases, laboratory tests showed hypoglycemia and high tolerance for dextrose. In most of the cases, there was either hypochlorhydria or achlorhydria. In many cases x-ray examination

revealed spasm of the ileocecal sphincter with stasis in the ileum and marked dilation. In such cases, there was usually some tenderness in that region.

COMMENT

This series of cases might be enlarged by further delay in making this report, but I feel that the present number is sufficient to demonstrate the picture of insufficiency of the suprarenal glands. The principal lack, of course, is in the scarcity of autopsy reports. This will, no doubt, be remedied in time after attention has been directed to the suprarenal glands. Another important feature of the study of this disturbance will be the observation of treated patients during the coming summer and fall. Will they revert to their former state, and if they do, will epinephrine again benefit them? Also, what changes in living habits might avert these climatic effects? What part does this functional disturbance play in accounting for the general changes in people of all races so characteristic of life in the tropics and the Orient? It will take time to answer these questions, and, since I am returning to America in June of this year, the present report is submitted in the hope that it will aid in the final solution of the larger problem of climatic effect on man. This is not a problem only of the tropics and the Orient, however, as it is likely to present itself anywhere in subtropical lands where heat and humidity present coincidental and sustained maxima. With the present intensive commercial development of such countries, it becomes important that a survey of them be made with this climatic effect in mind.

The prompt and beneficial action of epinephrine in almost all the cases in which it was tried throws important light on the nature of the disturbance. This in itself is not, of course, direct proof that there is suprarenal insufficiency. It is strongly suggestive that such is the case, however, and becomes still more important when considered in the light of the type of disturbances present and the autopsy observations in the second case presented.

In most instances the epinephrine was given orally according to the following prescription:

	Gm or Cc
R. Solution of epinephrine hydrochloride	20
Dextrose	30
Syrup of citric acid	10
Distilled water—sufficient to make	100
5 cc to be given orally half hour before meals	

The use of dextrose is based on the observations in Germany⁹ that it prevents oxidation of the epinephrine. In a few instances epinephrine

⁹ Unna, P. G. *Dermat. Wehnschr.* 75:685, 1922, abstr. of *Ars Medica*, 1922, vol. 12, p. 406, which contained a review of "Lehrbuch der Organotherapie" by Wagner von Jaureg and Gustav Bayer.

solution (1 1,000) was given sublingually in from 0.5 to 1 cc dosage, and in two cases it was given subcutaneously. Whether given according to the foregoing prescription or sublingually, the effect seemed just as satisfactory as when it was injected, in fact, the oral administration seemed preferable in that it did not cause systemic cardiovascular or metabolic disturbances of any kind. In two instances of hypersusceptibility to epinephrine, there was rather severe gastric pain from ten to twenty minutes after the dose of 5 cc had been swallowed. The pain lasted about twenty minutes, and was not followed by further unpleasantness. Smaller doses of 3 cc were well tolerated by these two patients.

Many physicians doubt the effectiveness of epinephrine given orally, but the belief that such doubt is unfounded is growing among critical observers. The principal point to bear in mind is that the effects of the drug given orally may be different from those following its use by injection. By the latter method of administration, one may cause a considerable rise in blood pressure, a quickening of the pulse rate, and a marked relaxation of normal or spastic smooth muscle in other parts of the body. The blood sugar and consumption of oxygen are increased and blood clotting is quickened. Great prostration may be produced by a slight overdosage. When given orally, on the other hand, none of these reactions occur in normal animals or man. In case too large a dose is given, there may be gastric pain for from ten to twenty minutes presumably from an intense vasoconstrictive action on the gastric mucosa, but one sees none of the changes in the body that follow injection. These facts were verified by Menninger,¹⁰ who used large doses (from 2 to 6 mg) mainly on patients with hyperthyroidism, who are usually most sensitive to epinephrine. He fell into the common error, however, of stating that the drug is unsatisfactory for oral use, because it does not produce any effects in people with good suprarenal function. He did not try it in a single case in which symptoms of suprarenal insufficiency were exhibited and in which effects would be more likely to be demonstrated. A normal person taking epinephrine orally according to the prescription given is not aware of any effects. Only in patients exhibiting a hypermotility or spasticity of the smooth musculature of the bronchioles, gastro-intestinal or genito-urinary tract are prompt effects obtained. In these cases, the inhibitory influence of the drug goes only so far as to reduce the motor function to a normal level. Thus in either severe spastic constipation or watery diarrhea, the oral administration of epinephrine causes only a return to normal function.

It was this inability to demonstrate such effects from epinephrine on laboratory animals that led Stewart¹¹ to attack the many clinical observa-

10 Menninger, W. C. Oral Administration of Epinephrine, *Arch. Int. Med.* 40:701 (Nov.) 1927.

11 Stewart, G. N. *Endocrinology* 5:283, 1921.

tions on suprarenal insufficiency The reply of Sajous¹² to Stewart emphasizes the point that failure to demonstrate a condition or result in normal animals does not necessarily vitiate observations made on disease conditions in man That suprarenal insufficiency as a clinical entity does exist is practically beyond doubt French writers¹³ recognized the condition as existing to some extent among troops during trench warfare, and obtained good results by the use of epinephrine Many of the symptoms described by them were similar to those seen in my patients, except that diarrhea was not mentioned as a frequent occurrence The point I wish particularly to stress is that this interference with suprarenal function may be widespread in its occurrence, perhaps to be classed as a major cause of disease rather than as a rarity Future studies may show that this effect of tropical heat is an important factor in determining the physical and mental characteristics of races subjected to such climatic influences

The conception of suprarenal function elaborated by Cannon¹⁴ that these glands fulfil emergency needs by quickly secreting epinephrine to stimulate the body would lead one to think that they would benefit in time of hot humid weather by obtaining a complete rest Such however, does not seem to be the case If the suppression is sufficient to produce symptoms, the recovery of function seems to be slow, so that patients may show increasing signs of insufficiency as the colder weather places a greater burden on the glands

A few months ago, I reported¹⁵ the occurrence of fatal reactions from insulin among Chinese patients with dosages as low as 4 units In view of these more recent observations of suprarenal insufficiency, it seems probable that this may supply an explanation of the insulin reactions Britton and Geiling¹⁶ found that the operation of medullectomy or the removal of the right suprarenal and denervation of the left, caused animals to be susceptible to insulin, convulsions coming on after as little as one tenth of the normally harmless dose An injection of epinephrine protected these animals against reaction to insulin Voigtlin and Dunn¹⁷ found the toxicity of insulin for white rats to be increased

12 Sajous, E de M *Endocrinology* **6** 198, 1922

13 Loeper, M, Beuzard and Wagner *Bull et mem Soc méd de hôp de Paris* **41** 903, 1917 Ramond F, and Francois, R *Ibid* **41** 1001, 1917 Josue O *Paris med* **19** 13, 1917 Carles, J *J de med de Bordeaux* **89** 185, 1918, abstr *J A M A* **71** 858 (Sept 7) 1918

14 Cannon, W B *Bodily Changes in Pam, Hunger, Fear and Rage*, New York, D Appleton & Company, 1918

15 Mills, C A *China M J* **41** 914, 1927

16 Britton, S W, and Geiling, E M K *Am J Physiol* **81** 467 1927

17 Voigtlin, C and Dunn E R *U S Pub Health Service, Pub Health Rep* 1923 p 1747

as the temperature under which the rats were kept was raised. These facts should serve as a warning against the unguarded use of insulin in the tropics or Orient or the free use of it such as one sees in American clinics.

Many textbooks on physiology state that sympathetic impulses cause constriction of the gastro-intestinal sphincters, with relaxation of the intervening segments of intestine. Shipley and Blackfan,¹⁸ however, showed that surviving strips of the musculature of the pylorus of newborn pigs and human infants are regularly relaxed by solutions of epinephrine *in vitro*. My results on patients also show a prompt and efficient relaxation of the various sphincters after the use of epinephrine orally. The conclusion seems justified that epinephrine in physiologic amounts serves only to cause relaxation throughout the gastro-intestinal tract. I have not found any reference to the use of epinephrine in the treatment of infants with pylorospasm. A trial of such usage would seem indicated.

As to the mechanism of the action of epinephrine in dysmenorrhea and menorrhagia, nothing definite is known.

SUMMARY AND CONCLUSIONS

1 A functional disturbance common in the tropics and Orient is described and illustrated by a report of forty cases seen during the last few months. The principal features of the disturbance are (a) hypermotility of the gastro-intestinal tract, with frequent occurrence of cardiospasm, pylorospasm and ileocecal or sigmoid spasm, (b) these motor disturbances may lead to nausea, vomiting, epigastric or abdominal pain and either diarrhea or constipation. The pain and other symptoms may simulate chronic appendicitis, peptic ulcer or tuberculous enteritis, and (c) there is also usually present gastric hypochlorhydria or achlorhydria, marked vascular hypotension and moderate anemia. Hypoglycemia with high tolerance for dextrose, weakness and loss in weight, urticaria edema, pigmentation of the skin and menorrhagia also were observed.

2 Foreigners are more susceptible to this trouble than the natives.

3 It seems to be definitely related to the coincidental peaks of humidity and heat, when cooling of the body becomes difficult. In some of the foreigners, the onset of trouble was clearly associated with their first contact with the intense humid heat, while in many others the onset followed their first summer in China.

4 Relief of the symptoms by the oral administration of epinephrine was usually immediate and complete.

18 Shipley, P. G., and Blackfan, K. D. Bull. Johns Hopkins Hosp. **33** 159, 1922.

5 Autopsy in one case did not show anything to account for the severe condition except changes in the supraenals characteristic of those seen in animals subjected to moist heat

6 The conclusion seems justified that supraenal insufficiency is responsible for the clinical picture presented, and that this represents a distinct disease entity just as truly as does hypothyroidism or hyperthyroidism

7 Subsidiary conclusions to be drawn from this report are (a) diagnosis of tuberculous enteritis, peptic ulcer or chronic appendicitis should be made with due caution to rule out all purely functional disturbances, (b) as a treatment for spastic constipation, the oral administration of epinephrine seems effective and often curative, and (c) many patients with so-called sprue are possibly suffering from suprarenal insufficiency

ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS

III THE ABSORPTION OF UNALTERED EGG PROTEIN IN ADULTS³

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The technic adopted for studying the absorption of unaltered egg protein was similar to that employed in the previous study of fish absorption¹ Egg was excluded from the subject's diet on the day of passive local sensitization, which was accomplished by the intradermal injection of about 0.05 cc. of the K egg serum. The egg meal was usually taken the following morning on an empty stomach. The reaction times were recorded in the same manner as in the previous studies.

The serums used in these studies, K₄, K₅ and K₆, were taken on three different occasions from the same egg-sensitive patient, whose history has already been described in the first communication² While samples K₅ and K₆ were slightly weaker in reagin content than K₄, they were all used interchangeably in these studies, as the differences between them were not considered sufficiently great to alter the results materially. Most of the tests were done with K₄. The 1:10 dilution was employed for reasons already noted in the previous communication.

The protein meal in the earlier tests usually consisted of one raw egg. In later studies, when it was found that the serum did not contain reagins for the egg yolk, only the egg white was used. The egg was swallowed unaltered or beaten up in a small amount of milk. The use of diluents or the amount employed did not seem materially to alter the results. The largest amount of diluent employed was from 4 to 6 ounces (118.4 to 178 cc.) (an eggnog or egg malted milk). The usual amount was 1 or 2 ounces (30 or 59 cc.) of milk. Whenever possible, the diluent was avoided.

The subjects selected for study in this series were almost all patients in hospitals. While some patients with gastro-intestinal diseases were included, most of the subjects were free from such disturbances. The diagnoses in each case are noted in table 1. With only one or two excep-

³ From the Jewish Hospital of Brooklyn, and from the Department of Bacteriology and Immunology, Division of Immunology, Cornell University Medical College and the New York Hospital.

¹ Brunner, M., and Walzer, M. Arch. Int. Med. **42**: 172 (Aug.) 1928.

² Walzer, M. J. Immunol. **14**: 143, 1927.

tions, these patients were tested when free from fever. Members of both sexes were included in the series. All but two of the subjects were adults. The youngest studied was 12 years of age.

RESULTS OF TESTS

The reaction times and results of the tests are tabulated in table 1. When the exact reaction time was not obtained on the reading was not

TABLE 1—Data of Tests in Each Case

Case No.	Date	Age	Sex	Diagnosis	Sensitizing Serum	Protein	Meal	Reaction Time In Minutes	
								Un diluted Serum	Dilution 1 10
1	2/15/26	60	M	Gastric carcinoma	K ₄	Egg	in 1 oz milk		45
2	2/15/26	37	M	Gonorrheal arthritis	K ₄	Egg	in 1 oz milk		80
3	2/15/26	48	M	Pneumonia convalescent	K ₄	Egg	in 1 oz milk		50
4	2/15/26	51	M	Cardionephritic syphilis	K ₄	Egg	in 1 oz milk		45
5	2/15/26	38	M	Cardiac decomposition	K ₄	Egg	in 1 oz milk		50
6	2/15/26	36	M	Duodenal ulcer	K ₄	Egg	in 1 oz milk		0
7	2/15/26	17	M	Ulcerative colitis	K ₄	Egg	in 1 oz milk		43
8	2/15/26	30	M	Pyelonephritis	K ₄	Egg	in 2 oz milk		60
9	2/15/26	34	F	Hypertension	K ₄	Egg	in 2 oz milk		45
10	4/14/26	36	F	Enterocolitis	K ₄	One white of egg			26
11	4/14/26	51	M	Gastric carcinoma	K ₄	One white of egg			10
12	4/14/26	44	M	Gastric ulcer	K ₄	One white of egg			45
13	4/14/26	45	M	Suppuration of kidney	K ₄	One white of egg			130
14	4/14/26	50	M	Osteosarcoma of rib	K ₄	One white of egg			0
15	5/27/26	12	M	Endocarditis	K ₄	One white of egg			100
16	5/27/26	32	M	Cerebrospinal syphilis	K ₄	One white of egg			0
17	5/27/26	40	F	Cholecystitis	K ₄	One white of egg			50
18	6/ 7/26	28	M	Acute rheumatic fever	K ₄	One white of egg			91
19	6/ 7/26	58	M	Hepatic cirrhosis	K ₄	One white of egg			45
20	6/ 7/26	23	F	Psychasthenia	K ₄	One white of egg			0
21	6/ 7/26	25	F	Hypertthyroidism, chole-					
				cystitis	K ₄	One white of egg			30
22	6/ 7/26	39	F	Polycythemia	K ₄	One white of egg			90
23	6/ 7/26	50	F	Hypertension and cholecystitis	K ₄	One white of egg			30
24	7/ 2/26	49	M	Asthma, achlorhydria	K ₆	One egg			30
25	8/21/26	22	F	Asthma	K ₆	White of egg in 1 oz of milk		50	55
26	9/ 3/25	55	F	Gastric carcinoma	K ₄	Egg	in 4 oz milk		
27	4/17/26	37	M	Hookworm	K ₄	2 eggs			
28	8/25/25	Adult	M	Lichen planus	K ₄	One egg			
29	8/25/25	Adult	M	Acrodermatitis atrophicans	K ₄	One egg			
30	1/27/26	Adult	M	Acrodermatitis atrophicans	K ₄	One egg			
31	10/20/25	Adult	M	Psoriasis	K ₄	One egg			
32		32	M	Normal	K _{4,5,6}	One egg		45	48*
33		44	M	Normal	K _{4,5,6}	One egg		30	30*
34	6/10/26	38	F	Normal	K ₆	One egg		33	

* The average of several tests

considered trustworthy, the positive reaction was designated by a + sign, 0 designated a failure to react. The results of the entire series are summarized in table 2.

It will be noted that the results in this series are similar to those obtained in the studies with fish proteins not only in the total percentage of positive reactions with each dilution but in the relative percentages of positive reactions with the various dilutions. In both series, the undiluted serum gives a slightly higher percentage of positive reactions than the 1:10 dilution.

Of the five patients who failed to react, four were not tested with the undiluted serum. Had it been possible to do this, it is probable that the percentage of cases demonstrating the reaction would have been even higher than has already been noted. Only two of the five patients giving negative reactions were tested by local intradermal injection of an egg solution into the serum site to determine whether they had been successfully sensitized. Both gave marked local reactions, thus ruling out failure to accept passive local sensitization as an explanation for the negative results of the test. In view of the consistently positive reactions when patients were tested locally in the studies with fish proteins, the routine local testing of patients giving negative reactions in the present series was not strictly adhered to. Failure to accept local passive sensitization with the K egg serums seemed highly improbable, as those types of cases in which this was apt to occur were not included in the present series (see the first paper of this series²).

TABLE 2—*Summary of Results of Tests*

	Un diluted	1 10 Dilution
Number of patients tested with each dilution	10	23
Number of patients demonstrating absorption phenomenon with each dilution	9	23
Percentage of patients demonstrating the phenomenon with each dilution	90	82.1
Total number of patients in series		34
Total number of patients failing to manifest the phenomenon		5
Percentage of patients demonstrating the absorption phenomenon		85.3

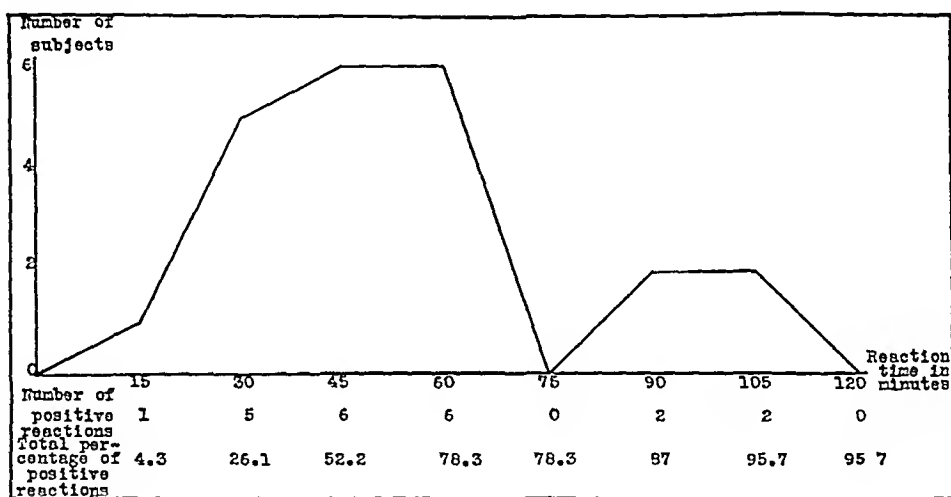
REACTION (ABSORPTION) TIME

The reaction times in the patients in this series were graphically represented, as shown in the accompanying illustration. Only the results with the 1:10 dilution were thus tabulated, as the patients tested with the undiluted serums were too few in number to be of service in this respect.

Of the twenty-three positive reactions occurring with the 1:10 reaction, only one (4.3 per cent) occurred in the first fifteen minutes. This is in sharp contrast to the reaction time in the patients tested with fish proteins, in which 32 per cent occurred within this period. In the second, third and fourth fifteen minute periods, there were five, six and six reactions, respectively. Therefore, eighteen of the twenty-three reactions, or 78.3 per cent, occurred within the first hour. In the patients tested with fish proteins, 86.3 per cent of the reactions had occurred within half that time, thus indicating a definitely slower absorption of unaltered egg protein than of fish. The average reaction time in the series tested with egg protein was about fifty-six minutes. That of the series tested with fish serum was about twenty minutes.

FACTORS AFFECTING REACTION TIME

The same factors affecting the absorption in the studies of the patients tested with fish were found to apply in the series tested with egg as well. The administration of other food before the ingestion of egg definitely prolonged the reaction time. This was well illustrated in patients 4 and 5, who were first given the yolk of eggs. As reagents for egg yolk are not present in the K egg serum, reactions did not result. After ninety minutes, a whole egg in 1 ounce of milk was given to each. In this instance, the patient in case 4, whose normal reaction time was forty-five minutes, reacted in ninety-three minutes. The reaction time in case 5 was similarly increased from fifty to ninety-five minutes. The local reactions in both were considerably less active than when tested under routine circumstances, that is, when the egg white was taken on a fasting stomach.



Graph representing reaction (absorption) times of the twenty-three patients sensitized with a 1:10 dilution of serum who demonstrated the absorption of unaltered egg protein.

It seemed of interest to determine the effect of peptone taken before the protein meal on the degree and rapidity of the reaction. The work of Pagniez and Vallery-Radot³ and other French writers suggests the use of 0.5 Gm of peptone given from one-half to one hour before meals as a preventive in those cases of allergy due to food sensitivities. As these conditions are due to absorption of protein in its unaltered state, it seemed important to determine, if possible, the effect of peptone on the phenomenon. Three subjects whose normal reaction times were known were therefore given capsules containing 0.5 Gm of Witte's peptone siccum from forty-five to sixty minutes preceding the egg protein

³ Pagniez, P. and Vallery-Radot, P. *Presse med* 24: 529, 1916

meal As a result of this, in case 4, the reaction time was increased from forty-five to ninety-three minutes, in case 3, it was reduced from fifty to twenty minutes, in case 17, it remained unaffected The use of peptone, moreover, seemed not to have a consistent effect on the degree or severity of the local reaction There did not seem to be any evidence, therefore, that peptone administered in the manner described influenced the absorption of unaltered protein in any definite manner

ABSORPTION OF UNALTERED PROTEIN FROM THE RECTUM

Nine of the cases tested in table 1 were studied for the purpose of determining whether absorption of unaltered protein from the rectum could be detected by the same technic as that employed for proteins administered orally

TABLE 3—Results of Rectal Administration of Protein

Case	Date	Age	Sex	Diagnosis	Sensitizing Serum	Preliminary Preparations	Protein Rectally Administered	Reaction Time in Minutes				Oral Reaction Time
								Undiluted Serum	Diluted 1:5	Diluted 1:10	Diluted 1:10	
7	2/15/26	17	M	Ulcerative colitis	K ₁		1 egg white in 2 oz milk				7	43
	4/17/26				K ₁		1 egg white in 2 oz milk				26	
10	4/17/26	36	F	Enterocolitis	K ₁	Test preceded by enema	1 egg white in 2 oz water				65	26
12	4/17/26	41	M	Gastric ulcer	K ₁	Test preceded by enema	1 egg white in 2 oz water				±*	45
13	4/17/26	45	M	Suppuration of kidney	K ₁	Test preceded by enema	1 egg white in 2 oz water		0			130
16	6/10/26	32	M	Cerebrospinal syphilis	K ₁	Test preceded by enema	1 egg white in 2 oz water		0			0
23	6/10/26	50	F	Hypertension, cholecystitis	K ₁	Test preceded by enema	1 egg white in 2 oz water		±*			30
22	6/10/26	39	F	Polycythemia	K ₁	Test preceded by enema	1 egg white in 2 oz water		54			90
25	8/23/26	22	F	Asthma	K ₂	Test preceded by enema	1 egg white in 2 oz water	75		125		55
27	4/20/26	30	M	Hookworm	K ₁	Test preceded by enema	2 eggs in 2 oz of water	0		0		0

* ± Indicates a slight reaction with slight erythema and slight pruritus without formation of wheals

Preparation of the patient and sensitization were accomplished as before The egg was administered by rectal tube, either unaltered or diluted in water or milk In some cases, an enema was given before the rectal feedings, to clean out the lower bowel The results in each case are noted in table 3

The patients in cases 16 and 27, who failed to exhibit a positive reaction following oral administration of the egg, gave negative results with the rectal feeding as well (In case 27, the patient has already been pointed out in the previous communication as the one who failed to demonstrate the reaction to both fish and egg when given orally, rectally or enterally) The patient in case 13, who showed a delayed reaction time after oral administration, failed entirely to exhibit the phenomenon following rectal administration The patient in case 7, who had large

ulcerative areas in the sigmoid and colon, exhibited a much more rapid and active reaction with the rectal than with the oral administration. The first test, made while the ulcerative process was acute, resulted in a marked positive reaction in seven minutes. The oral reaction time was forty-three minutes. With the inflammatory process subsiding, the rectal test was repeated two months later, the reaction this time appearing in twenty-six minutes. Case 22 was another in which the reaction time after rectal administration was more rapid than that by mouth. In cases 12 and 23, the local reactions following rectal administration were extremely mild, consisting of erythema and slight itch. In case 12, they were decidedly tardy in appearance, coming on as late as three and seven hours, respectively, in two instances. In cases 10 and 25, the reaction times after rectal administration were slightly longer than the oral.

Judging from the foregoing results, it would seem that absorption of unaltered protein generally occurs to a less degree from the rectum than from the upper digestive tract. It is also apparent that failure to demonstrate the phenomenon following oral administration of the protein under routine conditions is not necessarily to be considered as the result of some local factors in the upper digestive tract, such as hyperacidity and delayed emptying of the stomach. For it is noted that those showing delayed or absent reactions following oral ingestion usually do not show absorption from the rectum. The trait is therefore a constitutional rather than a local one or, if it involves the intestine itself, affects the entire alimentary system. The foregoing experiments, however, demonstrate beyond a doubt that rectal absorption of unaltered protein does occur in detectable quantities in most persons.

SUMMARY

1 The absorption of detectable amounts of unaltered egg protein from the digestive tract was noted in 85.3 per cent of thirty-four subjects tested and may therefore be considered a normal phenomenon.

2 The unaltered egg protein was detected in the blood stream in the first fifteen minutes in only one case, or 4.3 per cent. Twenty-six and one-tenth per cent of the reactions occurred within the first half hour, and 78 per cent within the first hour.

3 The same factors affecting the absorption time of fish protein affected that of egg protein as well.

4 Absorption of unaltered egg protein from the rectum was demonstrated in most cases in which it had occurred after oral administration. Patients who showed diminished or negative absorption after oral administration usually failed in the rectal test. This indicated that negative reactions usually could be attributed to a constitutional rather than a purely local cause.

5 Absorption from the rectum was usually somewhat slower and less pronounced than that from the upper enteral canal.

PERITONITIS

IV PRODUCTION OF ACTIVE IMMUNITY AGAINST THE FATAL OUTCOME OF EXPERIMENTAL FECAL PERITONITIS *

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AND

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In a previous communication,¹ it was shown that active immunity can be produced in dogs against a fatal outcome following "colon bacillus-gum tragacanth" peritonitis. Since one of the more common causes of peritoneal infection is soiling of the peritoneum by intestinal contents, this investigation was undertaken to determine whether active immunity can also be developed against a fatal outcome in this type of peritonitis. Since colon bacillus is found with and without other organisms in a high percentage of cases of peritonitis due to rupture of the appendix or perforation of intestines, it was determined to investigate the capacity of the colon bacillus alone to produce active immunity against the fatal outcome of fecal peritonitis.

EXPERIMENTAL METHOD AND EXPERIMENTS

Method—In preliminary experiments, it was found that the intraperitoneal injection into a dog of a saline suspension of 5 Gm of solid feces from the lower portion of the small intestine or from the large intestine of another dog invariably produced severe serohemorrhagic and fibrinopurulent peritonitis, which always proved fatal. This amount was therefore adopted in the following experiments as the standard for the production of fatal fecal peritonitis.

In order to produce immunity, colon bacilli were injected intraperitoneally into dogs by the following method. Living organisms were used for purposes of immunization in one series of animals and in another, dead organisms were used. The dead colon bacilli were produced by heating the saline suspension of the living organisms at 58 C for one hour. Cultures made of the heated suspensions proved sterile.

* Aided by a grant from the American Medical Association.

¹ From the Division of Laboratories and Research, Toledo Hospital, Toledo, Ohio, and the Department of Pathology, School of Medicine, Western Reserve University, Cleveland.

1 Goldblatt, H., and Steinberg, B. Peritonitis. III. Active Immunization Against Experimental B. Coli Peritonitis, Arch. Int. Med. **41**: 42 (Jan.) 1928.

Four intraperitoneal injections were given, the interval between successive doses being four days. The initial injection consisted of the saline washings of one agar slant of the organisms and the remaining three injections of two, three and four agar slants, respectively. This is exactly the same procedure that was employed in a previous investigation¹. On the fifteenth day after the last injection, the presence of immunity was tested by the intraperitoneal injection of 5 Gm. of solid feces suspended in 15 cc. of 0.9 per cent sodium chloride solution. As a control of the experiment, a similar injection of feces was given at the same time to nonimmunized normal dogs. Smears of the feces used showed abundant and varied bacteria which included relatively many large and small gram-negative bacilli, gram-positive diplococci and a few large gram-positive bacilli. Colon bacilli were identified by cultural methods, but no attempt was made to identify all the other organisms.

Immunization with Living Colon Bacilli—Eleven dogs were immunized with living colon bacilli by the foregoing method, group A (six dogs) at one time, and group B (five dogs) at another time. On the fifteenth day after the last immunizing injection, the animals were given the intraperitoneal injection of fecal material. For from twelve to thirty-six hours they showed varying degrees of malaise and vomited frequently. Of the six animals in group A, all survived, of the five in group B, four survived, and one died in forty-eight hours. Thus, of the total of eleven dogs, ten survived. One died in forty-eight hours, and autopsy revealed a severe serous and fibrinopurulent peritonitis.

Four days after the fecal injection, one of the animals of group A, clinically completely recovered, was killed, and autopsy showed the presence of some free pus in the peritoneal cavity with some fibrinopurulent exudate on the visceral and parietal peritoneum. One month after the injection of the feces, another dog of group A, at the time in excellent condition, was killed, autopsy did not show any gross abnormalities of the peritoneum. Six weeks after the injection of feces, one dog of group B was killed, and autopsy showed only a few fibrous adhesions between the upper surface of the liver and the under surface of the diaphragm. The remainder are still alive several months after the injection of the feces.

Immunization with Dead Colon Bacilli—Eight dogs were immunized with dead colon bacilli by the method described, group A (six dogs) at one time, and group B (two dogs) at another time. Fourteen days after the last immunizing injection, the animals were given an intraperitoneal injection of the fecal material. In this series, the fecal injection was made in groups A and B on the same days and with the same fecal material used for groups A and B of the series immunized with living colon bacilli. Of the six dogs in group A two survived and of the two

in group B, one survived. Of the total of eight dogs, therefore, three survived and were still living several months later. The remaining five dogs died in from twenty-two to sixty hours following the fecal injection. All of the dogs were ill. Those that survived had severe malaise, and vomited for from twelve to twenty-four hours. For the next two days the animals refused solid food and were somewhat lethargic, but from that time on, the return to normal was rapid and complete. The dogs that did not recover continued to vomit, were finally prostrated and were comatose for several hours before death. Autopsy showed severe serohemorrhagic and fibrinopurulent peritonitis.

A Injection of Fecal Material into Nonimmunized Normal Dogs—Fifteen normal dogs (six in group A, and nine in group B), were given the intraperitoneal injection of feces on the same day and with the same

Active Immunization Against a Fatal Outcome of Experimental Fecal Peritonitis in Dogs

Number of Dogs	Immunizing Agent	Outcome
11 (group A — 5) (group B — 6)	Living colon bacilli	10 survived (group A — 4) (group B — 6) 1 died in 48 hours (group A)
8 (group A — 6) (group B — 2)	Dead colon bacilli (killed by heat)	3 survived (group A — 2) (group B — 1) 5 died in from 22 to 60 hours (group A — 4) (group B — 1)
15 (group A — 6) (group B — 9)	None	15 died in from 12 to 24 hours
3 *	None	3 survived

* The fecal material used for this group was sterilized by heat

material used for groups A and B of the series immunized by living and dead bacilli. All of the dogs died in from twelve to twenty-four hours. Autopsy showed severe hemorrhagic serous and fibrinopurulent peritonitis.

Smears of the peritoneal exudate of these dogs showed similar organisms to those seen in the feces used for injection, namely, small and large gram-negative bacilli, gram-positive cocci and large gram-positive bacilli. Smears of the peritoneal exudate from the immunized dogs that died showed similar organisms. Similar organisms were also recovered in cultures, but no attempt was made to identify any except colon bacilli which were present in abundance.

B Injection of Heated Fecal Material into Nonimmunized Normal Dogs—To test the effect of the feces, independent of living organisms, three animals were given intraperitoneal injections with the standard amount of saline suspension of fecal material which had been heated for one hour at 60 C. This was a portion of the feces used for groups B

Cultures of the heated feces proved sterile. The three animals survived. One was killed seventy-two hours after the fecal injection, and autopsy did not reveal any gross peritoneal lesion.

COMMENT

It is apparent from the results of these experiments that it is possible to prevent the fatal outcome of fecal peritonitis in dogs by active immunization with living colon bacilli. In this communication, no explanation is offered for this phenomenon. Whether death in fecal peritonitis is entirely due to the action of the colon bacillus and the active immunization with these organisms results in the production of specific antibodies or protective cellular reaction, or whether the immunity produced by *Bacillus coli* is nonspecific, and of cellular or humoral nature, or both, remains an open question.

The experiments in which colon bacilli, killed by heat, were used to produce immunity showed protection in a small percentage of the animals. This would indicate that dead organisms might be employed for the production of active immunity against a fatal outcome in fecal peritonitis, but that heat destroys a great part of the antigenic power of the organisms. Other methods of killing the bacteria are being employed for the further investigation of active immunization with dead colon bacilli against the fatal outcome of fecal peritonitis.

SUMMARY AND CONCLUSIONS

1 The intraperitoneal injection into fifteen normal dogs of 5 Gm of solid feces suspended in 15 cc of physiologic sodium chloride solution invariably resulted in the production of severe serous and fibrinopurulent peritonitis which always proved fatal.

2 Active intraperitoneal immunization with "living" colon bacilli resulted in the survival of ten of eleven dogs after an intraperitoneal injection of feces.

3 Active intraperitoneal immunization with "dead" colon bacilli, killed by heat, resulted in the survival of three of eight animals after an intraperitoneal injection of feces. Killing by heat greatly diminishes the antigenic power of colon bacilli.

4 Heated feces did not produce peritonitis, and the three dogs into which this substance was injected survived. The bacteria of fresh feces are therefore necessary for the production of peritonitis and the fatal outcome.

RELATIVE LYMPHOCYTOSIS IN HYPERTHYROIDISM *

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BOSTON

In 1908, Kocher ¹ pointed out that the differential formula in cases in which patients were suffering from exophthalmic goiter might be abnormal, showing a preponderance of lymphocytic elements. He thought that this relative lymphocytosis represented an index of the severity of the disease. In a recent communication,² I reported on the production of a relative mononucleosis in normal animals, occurring after a period of excitement lasting from ten to fifteen minutes. This emotional relative mononucleosis was evidently connected with sympathetic activation of lymphoid structures, particularly the spleen, for it was shown that removal of the sympathetic strands in an animal, splenectomy, or merely denervation of the spleen could inhibit this physiologic increase in the relative mononuclear counts after excitement.

The present clinical study was undertaken in order to ascertain the incidence of relative lymphocytosis in cases of hyperthyroidism, and also the character of the differential formula in patients who have recovered or who have a normal basal metabolism after subtotal or partial thyroidectomy has been performed. Through such a study it was thought that a correlation might be made between the experimental observations already mentioned on the production of a relative emotional mononucleosis and the clinical symptoms in exophthalmic goiter in which the sympathetic system is presumably overstimulated.

INCIDENCE

One hundred cases of hyperthyroidism were collected from the records of the Peter Bent Brigham Hospital. In sixty-seven cases the patients showed a definite relative lymphocytosis of 30 per cent or more (table). Fifty-six per cent of the 100 patients in this series had signs of exophthalmos. Eighty per cent of this group, namely, those having hyperthyroidism and exophthalmos, showed a definite relative lymphocytosis. In the group of patients having hyperthyroidism as revealed by the clinical picture and the basal metabolism but without signs of exophthalmos, only 50 per cent showed a definite relative lymphocytosis (table). It would seem as if a relative lymphocytosis is somewhat more

* From the Medical Service of the Peter Bent Brigham Hospital.

1 Kocher, T. Blutuntersuchungen bei Morbus Basedowii, Arch f klin Chir **87** 131, 1908.

2 Menkin, V. Emotional Relative Mononucleosis, Am J Physiol **85** 489, 1928.

Percentage of Lymphocytes in One Hundred Cases of Hyperthyroidism

Hyperthyroidism With Exophthalmos,		Hyperthyroidism Without Exophthalmos,	
Case No	Percentage of Lymphocytes	Case No	Percentage of Lymphocytes
24890	43	18932	31
20351	52	20364	60
20751	40	20632	32
20792	42	20641	31
21069	34	20758	31
21080	32	21243	32
22017	33	22302	43
22256	35	22331	33
20315	45	22369	23
21626	46	20270	21
22560	44	19829	29
20022	33	21174	26
18974	48	22150	19
18955	22	18872	15
18975	28	29946	30
23794	46	29860	26
22275	24	30447	18
18893	18	30610	33
20848	12	30585	41
25017	30	30135	30
25073	51	29499	20
25035	43	30686	35
25367	49	25092	25
25 21	33	24953	40
26051	34	25360	52
26080	20 (slight)	25769	25
26151	46	26106	28
26342	45	25936	26
22963	44	27036	27
238 2	37 (slight)	27019	18
22781	42 (lid lag only)	23042	29
23068	31	23260	32
23524	42	23588	48
23576	27	24104	20
23469	39	23970	54
23937	48	29606	20
23871	34	29489	40
24012	52	29499	20
24184	38	29792	30
24377	26	25554	32
23815	52	C W	18
29729	57	E O	34
29680	23 (slight)	G H	20
29034	43 (slight)	E G	14
28896	20		
E B	25		
E1 G	41		
C B	48		
E S	47		
D R	42 (slight)		
E H	45		
E R	42 (lid lag only)		
W L	52		
B	51		
R M	32		
	39 (lid lag only)		
Average	38%	Average	30%
Total number of cases		Hyperthyroidism With Exophthalmos	Hyperthyroidism Without Exophthalmos
Number of cases with relative lymphocytosis (30 per cent or more)		56	44
Percentage with relative lymphocytosis		45	22
		80	50

prone to occur in cases of hyperthyroidism exhibiting also exophthalmos than in cases having hyperthyroidism, but without abnormal eye signs. This fact is suggestive in view of a possible generalized sympathetic activation of lymphoid structures in cases in which exophthalmos is superimposed on the hyperthyroidism.

DIFFERENTIAL FORMULA AFTER THYROIDECTOMY

As pointed out in the foregoing, relative lymphocytosis is more apt to be found in patients having definite exophthalmos in addition to other signs of hyperthyroidism. Will this abnormal blood picture disappear after subtotal thyroidectomy, or is the condition associated with a concomitant hyperplasia of lymphoid structures bearing no direct relationship to the thyroid gland? The present study was undertaken in an attempt to answer this question. Ten patients were followed up with the accompanying results in each case.

REPORT OF CASES

CASE 1—E B, a woman, aged 32, entered the Peter Bent Brigham Medical Service in November, 1923. The basal metabolism was +57. Exophthalmos was not present. The differential count showed polymorphonuclears, 68 per cent, lymphocytes, 26 per cent, eosinophils, 3 per cent. In December, a partial thyroidectomy was performed. In January, 1925, the patient was readmitted to the hospital with a basal metabolism of +51, and with marked exophthalmos. The differential count revealed polymorphonuclears, 52 per cent, lymphocytes, 41 per cent, large mononuclears, 7 per cent. Operation was again performed. In October, 1927, she reentered the hospital with a basal metabolism of +10. The differential count was polymorphonuclears, 80 per cent, lymphocytes, 15 per cent, large mononuclears, 4 per cent.

CASE 2—R B, a woman, aged 23, entered the hospital in June, 1927, with marked exophthalmos and a basal metabolism of +39. The differential formula was polymorphonuclears, 54 per cent, lymphocytes, 36 per cent, large mononuclears, 8 per cent, eosinophils, 1 per cent, basophils, 1 per cent. She reentered for follow-up in October, 1927. The basal metabolism was 0. The differential count revealed polymorphonuclears, 65 per cent, lymphocytes, 26 per cent, eosinophils, 4 per cent, basophils, 2 per cent, unknown, 3 per cent.

CASE 3—C B, a man, aged 35, entered the hospital in September, 1924, with marked exophthalmos and a basal metabolism of +76. The differential count showed polymorphonuclears, 44 per cent, lymphocytes, 47 per cent, large mononuclears, 9 per cent. Partial thyroidectomy was performed. The patient was readmitted to the hospital in October, 1927, the basal metabolism was +20, the differential count was polymorphonuclears, 63 per cent, lymphocytes, 27 per cent, large mononuclears, 8 per cent, eosinophils, 2 per cent.

CASE 4—E S, a woman, aged 49, was admitted to the hospital in November, 1923, with a basal metabolism of +12, without signs of exophthalmos. The differential count revealed polymorphonuclears, 70 per cent, lymphocytes, 26 per cent, large mononuclears, 3 per cent, eosinophils, 1 per cent. In October, 1924, slight exophthalmos was present, the basal metabolism was +32. The differential count showed polymorphonuclears, 56 per cent, lymphocytes, 42 per cent, large

mononuclears, 1 per cent, eosinophils, 1 per cent In October, 1927, the patient appeared entirely normal clinically The differential count showed polymorphonuclears, 69 per cent, lymphocytes, 22 per cent, large mononuclears, 8 per cent, eosinophils, 1 per cent

CASE 5—R D, a woman, aged 31, entered the hospital in July, 1925, with signs of exophthalmos and a basal metabolism of $+47$ The differential count revealed polymorphonuclears, 47 per cent, lymphocytes, 45 per cent, large mononuclears, 7 per cent, eosinophils, 1 per cent Thyroidectomy was performed In October, 1927, the patient entered the outpatient department for follow-up She seemed perfectly well The differential count showed polymorphonuclears, 60 per cent, lymphocytes, 29 per cent, large mononuclears, 7 per cent, eosinophils, 3 per cent, unknown, 1 per cent

CASE 6—E R, a woman, aged 32, entered the hospital in August, 1926, with a basal metabolism of $+59$, and with moderate exophthalmos The differential count was polymorphonuclears, 36 per cent, lymphocytes, 52 per cent, large mononuclears, 12 per cent Subtotal thyroidectomy was performed In November, 1927, the patient reentered for follow-up, she appeared to be well The differential count showed polymorphonuclears, 77 per cent, lymphocytes, 15 per cent, large mononuclears, 4 per cent

CASE 7—W L, a woman, entered the hospital in December, 1924, with moderate exophthalmos The differential count revealed polymorphonuclears, 45 per cent, lymphocytes, 51 per cent, large mononuclears, 4 per cent The basal metabolism was $+51$ The basal metabolism test in October, 1927, was -13 , and signs of postoperative myxedema were apparent On Nov 15, 1927, the differential count showed polymorphonuclears, 58 per cent, lymphocytes, 33 per cent, large mononuclears, 6 per cent, eosinophils, 3 per cent

CASE 8—C W, a woman, aged 42, entered the hospital without signs of exophthalmos, the basal metabolism was $+89$ on March, 1927 The differential count revealed polymorphonuclears, 74 per cent, lymphocytes, 18 per cent, large mononuclears, 8 per cent Subtotal thyroidectomy was performed in November, 1927, the basal metabolism was $+31$, the differential count showed polymorphonuclears, 70 per cent, lymphocytes, 22 per cent, large mononuclears, 6 per cent, eosinophils, 3 per cent

CASE 9—E O, a woman, aged 35, was admitted to the hospital in December, 1926 Exophthalmos was not present, the basal metabolism was $+29$ The differential count was polymorphonuclears, 56 per cent, lymphocytes, 34 per cent, large mononuclears, 10 per cent Thyroidectomy was performed In November, 1927, the differential count showed polymorphonuclears, 61 per cent, lymphocytes, 37 per cent, large mononuclears, 2 per cent

CASE 10—E H, a woman, aged 54, entered the hospital in December, 1926, with a basal metabolism of $+43$, exophthalmos was not present, but there was a lid lag The differential count revealed polymorphonuclears, 48 per cent, lymphocytes, 42 per cent, large mononuclears, 5 per cent, eosinophils, 4 per cent On Nov 8, 1927, the differential count showed polymorphonuclears, 55 per cent, lymphocytes, 41 per cent, large mononuclears, 4 per cent, eosinophils, 1 per cent

It is clear from cases 1 and 4 that a relative lymphocytosis tends to appear when exophthalmos is also present, and furthermore that this exophthalmos is apparently a later stage of the disease Though the patient in case 7 showed a reduction in relative lymphocytosis after

thyroidectomy was performed, a high relative lymphocyte count (33 per cent) was present. Emery³ has shown that a relative lymphocytosis is often seen in myxedema. The patient in this case showed a post-operative basal metabolism of -13 , hence it is conceivable that a relative lymphocytosis of 33 per cent may perhaps be part of a postoperative myxedematous blood picture.

The patient in case 8 did not show any signs of relative lymphocytosis before operation. It is interesting to note also that there was no sign of exophthalmos in this case (table). In cases 9 and 10, the patients both showed exophthalmos and relative lymphocytosis which, however, was not relieved by operation. The patients in the remaining six cases showed exophthalmos and a relative lymphocytosis before operation. The differential formula in this group became normal after thyroidectomy was performed.

COMMENT

From this study, it seems as though a relative lymphocytosis is a frequent occurrence in hyperthyroidism, especially in cases in which a definite exophthalmos is associated with the usual signs of the disease. It is difficult to conceive of the exact mechanism which produces this relative increase in lymphocytes. Capelle⁴ pointed out that in all severe cases of exophthalmic goiter there is a lymphoid hyperplasia. Marine and Lenhardt⁵ consider the changes in both the thyroid and the lymphoid tissues to be the truest indexes of the severity of the disease. Definite hyperplasia of the thymus seems to be present in 75 per cent of the cases.⁶ If exophthalmos is taken as an index of sympathetic overactivity resulting from thyroid intoxication, it is probable that the relative lymphocytosis of exophthalmic patients is caused by sympathetic stimulation of lymphoid structures, particularly the spleen causing a discharge of lymphocytes in the blood stream by an increase in splenic contractions. It has been shown that a similar mechanism takes place when a normal animal is excited for from ten to fifteen minutes.² Sympathectomy or denervation of the spleen tends to inhibit this physiologic relative mononucleosis in animals. Thyroidectomy in patients with exophthalmic goiter presumably removes a factor which stimulates the discharge of lymphoid elements into the blood stream. This would result in a sub-

3 Emery, E. S. The Blood in Myxedema, *Am J M Sc* **165** 577, 1923

4 Capelle. Die Beziehungen der Thymus zum Morbus Basedowii, *Beitr z klin Chir* **58** 353, 1908

5 Marine, D., and Lenhardt, C. H. Relation of Iodine to the Structure of Human Thyroids. Relation of Iodine and Histologic Structure to Diseases in General, to Exophthalmic Goiter, to Cretinism and Myxedema, *Arch Int Med* **4** 440 (Nov) 1909

6 McCarrison, R. The Thyroid Gland in Health and Disease, New York, William Wood & Company, 1917

sequent restoration of the normal differential formula. Evidently patients with hyperthyroidism and without exophthalmos represent a less toxic or generalized involvement. It is difficult to account for the relative lymphocytosis in cases 9 and 10 in which exophthalmos was not present and in which operation did not relieve the condition. It is possible that in these two cases, there was not a similar mechanism of sympathetic discharge from the spleen, but rather a concomitant lymphoid hyperplasia of the thymus, and perhaps other lymphoid structures which, by their increased activity, raised the level of relative lymphocytes in the blood stream. Removal of the thyroid or of the sympathetic strands presumably would not cause any decrease of such lymphoid activity.

SUMMARY

- 1 Relative lymphocytosis was observed in 67 per cent of the cases of hyperthyroidism.

- 2 Relative lymphocytosis is more frequently seen in patients who have exophthalmos superimposed on the usual clinical signs of hyperthyroidism.

- 3 In patients with exophthalmos, thyroidectomy decreases the relative lymphocytosis and restores a normal differential formula.

- 4 It is suggested that the relative lymphocytosis in cases of exophthalmic goiter is due to sympathetic stimulation of lymphoid structures, particularly of the spleen, which causes it to contract, as evidenced by experimental work reported in a previous publication.

- 5 Some patients with hyperthyroidism but without signs of exophthalmos show a relative lymphocytosis apparently not relieved by thyroidectomy. The mechanism of this type of relative lymphocytosis is not clear. It is suggested that it may be caused by a concomitant hyperplasia of lymphoid structures, such as the thymus.

It gives me pleasure to express my appreciation to Dr. Henry A. Christian for suggesting this problem and for valuable assistance in carrying it out.

PERNICIOUS ANEMIA

EDEMA AND REDUCTION IN EXCRETION OF WATER *

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It is well known that patients with pernicious anemia have a more or less pronounced tendency toward edema, and that they usually have edema, especially in the later stages of the disease. Edema has always been considered a link in the clinical symptomatology of this disease, but a closer study of its pathogenesis has been limited. In most instances, edema is understood to be nephrogenetic (Makarow¹), but it is also thought to be determined by extrarenal factors (Saltzman²). In both cases, the authors seem inclined to regard the anemia itself, the low hemoglobin percentage, as the determining factor.

Again, in patients with pernicious anemia, one finds a characteristic change in the excretion of water. Christian³ and Stieglitz⁴ stated that patients generally show a tendency toward fixation of the specific gravity of the urine without accompanying polyuria and with a relative increase of the nocturnal urine. Saltzman,² Essen and Porges⁵ substantiated this opinion and at the same time found a characteristic result with the water test, namely, a retarded excretion with a tendency toward fixation of the specific gravity at a comparatively high level. This change in the excretion of water is generally understood to be nephrogenetic. Christian³ and Stieglitz⁴ expressed the opinion that it is dependent on the anatomic changes in the kidneys, Essen and Porges,⁵ that it is due to deficiency of oxygen. Only Saltzman² spoke of the possibility of extrarenal factors being the cause of the changed excretion of water as well as the cause of the edema.

THE CLINICAL APPEARANCE OF EDEMA

In its localization, anemic edema resembles nephrotic edema to a certain extent. In both mild and severe cases, a diffuse puffiness of the face

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1 Makarow *Inaug Diss*, Jena, 1912

2 Saltzman *Finska lak-sällsk Handl* **61**:1, 1919

3 Christian *Renal Function in Anemia*, *Arch Int Med* **18**:429 (Oct) 1916

4 Stieglitz *Disturbances of Renal Function in Pernicious Anemia*, *Arch Int. Med* **33** 58 (Jan) 1924

5 Essen and Porges *Wien Arch f Inn Med* **5**:195, 1922

is noticeable, which often, to a great extent, gives patients with pernicious anemia a characteristic appearance. Edema of the lower extremities, and if the patient is in bed, edema of the lumbar region, is more or less definite. In extreme cases marked edema of the upper extremities is found especially in the hands. Most characteristic, however, is a peculiar diffuse retention of water in the integument and subcutaneous tissues.

In less pronounced cases, we have used the following procedure to determine "occult edema." We have placed a rubber tubing around the antibrachium and the crus and held it tight for two minutes. If there is "occult edema," a circular depression appears in the skin easily discernible to the eye and perceptible to the touch. This symptom of "occult edema" is often present in patients with pernicious anemia.

With regard to the frequency of edema in cases of pernicious anemia, 64 per cent of Cabot's⁶ patients and almost 50 per cent of Schauman's⁷ had edema. The frequency of finding edema, however, depends partly on what is understood as edema but mostly on the stage of the illness at which the patient was examined. We feel sure that if patients were followed until death, edema would be an almost constant symptom of the disease. A characteristic of the edema is that it appears during the relapses and disappears during the remissions. Its reappearance indicates, at a comparatively early stage, the occurrence of a new relapse.

REDUCED EXCRETION OF WATER AS DETERMINED BY THE WATER TEST

We have examined the excretion of water in thirty-five patients on whom ninety-six water tests were made (Examinations made before knowing liver treatment). Most of the patients were examined a number of times at different phases of the disease. One thousand grams of water were given the patient at 8 o'clock, and urine was passed at the times shown in tables 1 and 2.

A few cases will illustrate the typical change which occurs with the water test.

These tables show that the excretion of water is reduced considerably during the first four hours, and that the specific gravity is fixed near a rather high average. In these two cases albuminuria and cylindruria were not noted, the systolic blood pressure was 115 and 130, respectively, the excretion of thiosulphate, 33 and 27 per cent, respectively, and the blood urea was 27 and 44 mg per hundred cubic centimeters,

⁶ Cabot, in Osler and McCrae. *Modern Medicine*, vol 4, Philadelphia, Lea & Febiger, 1908.

⁷ Schauman. Schauman and Saltzman. *Die perniziose Anaemie*, Encyklop d Klin Med, Berlin, 1925.

respectively. The first patient did not show edema, the second patient had puffiness of the face, slight edema of the lumbar region and lower extremities and a positive reaction when the compression test was made on the upper and lower extremities.

In studying the results of the water test, the predominant impression is that the result of the test depends on whether the test was made during the period of relapse or during the remission. It is evident that patients first seen in a relapse often show a great reduction in the excretion of water in the beginning, when there is a remission, the excretion gradually improves and finally becomes normal.

TABLE 1—*Data Showing Water Excretion in M. A.*

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
2/1/26	35	7-8	30	1.018
		8-9	22	1.019
		9-10	40	1.021
		10-11	40	1.017
		11-12	40	1.015
		12-6	195	1.018
		6-7	15	1.021
		7-6	195	1.021
		6-7 next morning	15	1.021

TABLE 2—*Data Showing Water Excretion in L. M.*

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
5/20/25	42	7-8	15	1.022
		8-9	21	1.021
		9-10	58	1.017
		10-11	43	1.019
		11-12	29	1.023
		12-6	150	1.023
		6-7	12	1.024
		7-6	240	1.024
		6-7 next morning	20	1.016

The patient A. F. A. in table 3 is a typical example. Another example of this type is S. J., shown in table 4.

The exact reverse of this can be seen in table 5. When this patient, L. M., was discharged from the hospital, the excretion of water was normal, he had a relapse and when he returned there was a reduction in the excretion of water. These examples illustrate the fundamental principle.

In comparing the course of edema and the excretion of water, it can be said that they are usually simultaneous, that is, the edema and the reduced excretion of water are most noticeable during the severe stage of the illness. However, there is no congruity in evidence, because there can be noticeable edema at the same time that the water test

TABLE 3—Data Showing Water Excretion in A F A

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
5/18/25	25	7- 8	192	1 019
		8- 9	80	1 019
		9-10	142	1 019
		10-11	84	1 019
		11-12	44	1 020
		12- 6	Sum 350	
		6- 7		
		7- 6		
		6- 7 next morning		
			71	1 017
			70	1 012
		7- 8	21	1 019
		8- 9	68	1 019
		9-10	27	1 018
5/28/25	29	10-11	176	1 011
		11-12	170	1 009
		12- 6	Sum 441	
		6- 7		
		7- 6		
		6- 7 next morning		
			95	1 016
			26	1 021
		7- 8	125	1 017
		8- 9	110	1 011
		9-10	325	1 004
		10-11	330	1 004
		11-12	290	1 006
		12- 6	Sum 1055	
		6- 7		
		7- 6		
		6- 7 next morning		
6/ 5/25	46		34	1 019
			78	1 024
		7- 8	45	1 021
		8- 9	156	1 017
		9-10	415	1 007
		10-11	340	1 008
		11-12	250	1 008
		12- 6	Sum 1161	
		6- 7		
		7- 6		
		6- 7 next morning		
			18	1 022
			100	1 024
		7- 8		
		8- 9		
		9-10		
		10-11		
		11-12		
		12- 6		
		6- 7		
		7- 6		
		6- 7 next morning		
6/29/25	60	7- 8	45	1 021
		8- 9	156	1 017
		9-10	415	1 007
		10-11	340	1 008
		11-12	250	1 008
		12- 6	Sum 1161	
		6- 7		
		7- 6		
		6- 7 next morning		
			18	1 022
			100	1 024
		7- 8		
		8- 9		
		9-10		
		10-11		
		11-12		
		12- 6		
		6- 7		
		7- 6		
		6- 7 next morning		

TABLE 4—Data on Water Excretion of S J

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
9/27/24	49	7- 8	200	1 024
		8- 9	36	1 024
		9-10	55	1 022
		10-11	23	1 011
		11-12	40	1 017
		12- 6	Sum 154	
		6- 7		
		7- 6		
		6- 7 next morning		
			45	1 018
			0	
			0	
			32	1 023
		7- 8	104	1 018
10/30/24	81	8- 9	76	1 014
		9-10	470	1 004
		10-11	265	1 006
		11-12	72	1 016
		12- 6	Sum 885	
		6- 7		
		7- 6		
		6- 7 next morning		
			0	
			83	1 021
			0	
			24	1 021
		7- 8		
		8- 9		
		9-10		
		10-11		
		11-12		
		12- 6		
		6- 7		
		7- 6		
		6- 7 next morning		

shows a normal or almost normal result, and also the reverse. An example of the first case will be seen in table 6, in the patient concerning whom data are given, there was a slightly noticeable edema with a positive compression reaction on the arms and legs.

An example of a different course is shown in table 7 in a case in which the excretion of water was greatly reduced in spite of the lack of evidence of manifest or occult edema.

TABLE 5—Data on Water Excretion of L M

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
6/ 4/24	76	7- 8	104	1 019
		8- 9	212	1 007
		9-10	450	1 005
		10-11	180	1 007
		11-12	58	1 015
			Sum 900	
		12- 6	290	1 014
		6- 7	49	1 023
		7- 6	310	1 024
		6- 7 next morning	46	1 022
		7- 8	41	1 020
		8- 9	25	1 020
		9-10	44	1 020
3/ 5/25	40	10-11	52	1 018
		11-12	50	1 012
			Sum 171	
		12- 6	370	1 013
		6- 7	80	1 016
		7- 6	470	1 018
		6- 7 next morning	32	1 020

TABLE 6—Data on Water Excretion of J C

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
3/10/25	32	7- 8	86	1 013
		8- 9	315	1 004
		9-10	265	1 004
		10-11	57	1 013
		11-12	37	1 015
			Sum 774	
		12- 6		
		6- 7	26	1 016
		7- 6		
		6- 7 next morning	25	1 017

It seems that the excretion of water can give a more definite indication of the actual condition than the edema, which is either in a stage of development or in a stage of resorption.

CAUSES OF EDEMA AND REDUCTION IN THE EXCRETION OF WATER

Cardiac Insufficiency—In an article published in 1905, Kraus⁸ says that he tried to determine, by means of clinical and experimental

⁸ Kraus Berl klin Wchnschr, vol 4, 1905

data, the influence of fatty degeneration on the functional power of the heart. His attempt, however, was without much result. He concludes that "alles in allem müssen wir uns am Krankenbett doch wohl eher auf den Standpunkt derjenigen stellen, welche die degeneratio adiposa cordis, zumal bei gleichzeitig dauernd erhöhter Arbeit des Herzens, auch in den mittleren Graden mit Bezug auf die Leistungsfähigkeit keineswegs für völlig bedeutungslos halten" (Doubtless we must take the clinical attitude of those who consider degeneratio adiposa cordis [even though only a moderate degree], especially if associated with increased work of the heart, as exerting considerable influence on its performance.)

However, the question appears doubtful. Clinically, these patients do not have any positive indication of cardiac insufficiency, the dyspnea and tachycardia observed when the patient walks about are well accounted for by the lowered amount of hemoglobin with its accompany

TABLE 7—Data on Water Excretion of P N

Date	Hemoglobin Percentage	Time	Diuresis	Specific Gravity
1/19/25	42	7-8	55	1.017
		8-9	43	1.017
		9-10	50	1.019
		10-11	40	1.019
		11-12	36	1.019
		12-6	290	1.017
		6-7	36	1.019
		7-6	530	1.019
		6-7 next morning	78	1.016

ing lack of oxygen, and need not indicate a definite weakening of the heart muscle. When a patient is at rest and in bed, these symptoms are not evident in spite of definite edema. More important, however, is the fact that other stasis phenomena are lacking—hypostasis pulmonum, stasis hepatis and stasis renum. Furthermore, in its localization the edema does not resemble cardiac edema. It is more diffuse and often appears with edema of the face. We are prone to be reserved in placing too great stress on the influence of a weakened functional power of the heart in the pathogenesis of edema or the reduction of the excretion of water.

Nephropathy.—That edema or the reduction in the excretion of water may be caused by a renal disturbance is a possibility that has received much more attention, recently, the majority of those who have studied this question have come to the conclusion that the symptoms are renal. The fact is that the kidneys often are actually the site of slight pathologic anatomic changes sometimes accompanied by a slight change in the function of the kidney. Anatomically, the kidneys (Makarow,¹ Saltzman²) are seldom normal, and they are often the site of mild

parenchymatous as well as interstitial changes. As a rule, the changes are not definite, and they are comparatively seldom seen macroscopically. When seen, they consist of a slight shrinkage of the kidney, a slight roughness and granulation of its surface, a small adherent capsule and a rather small cortex. Microscopically a more or less extensive fatty infiltration of the epithelia, other degenerative processes in the epithelia and slight changes in the glomeruli with an increase in the interstitial tissue are found. In some cases, these changes are evident and pronounced, doubtlessly the reason for the former number of publications on the simultaneity of pernicious anemia and chronic nephritis. Saltzman² concluded that "The histological data indicates that in pernicious anemia nephrosis goes hand in hand with interstitial and glomeruli changes."

There are manifold data concerning the function of the kidneys. In the first place it is a long established fact that albuminuria, although mild and, as a rule, transitory, is often a symptom of the disease. There is, however, a difference of opinion concerning the frequency of albuminuria. It is most frequently reported by Cabot,⁹ who found albuminuria in 236 of 506 cases (40 per cent) and cylinduria in 119 cases (24 per cent). Saltzman² reported albuminuria in seven of eleven cases. He stated that it was not decidedly marked and was usually transitory, the greatest quantity observed being one per thousand.

Retention of nitrogen has been the subject of much research. Kahn and Barsky⁹ found a normal amount of nonprotein nitrogen and blood urea in three cases and a normal function of the kidneys as determined by the phenolsulphonphthalein test. Gettler and Lindeman¹⁰ examined thirty-two patients with pernicious anemia and found that in 12 per cent the amount of nonprotein nitrogen was over 60 mg per hundred cubic centimeters and that in 18 per cent, the blood urea was over 40 mg per hundred cubic centimeters. This high percentage was obtained from comparatively few cases. Essen and Poiges⁵ examined ten patients with pernicious anemia and found that the amount of nonprotein nitrogen was normal or nearly normal.

We examined the function of the kidneys in our patients partly by examining the urine for albumin and cylindroids, partly by the thio-sulphate test and partly by van Slyke's blood urea test. We also took the systolic blood pressure (Riva-Rocci).

Our examinations of the urine showed a slight trace of albumin, as a transitory phenomena, in eleven of thirty-seven patients, in the

9 Kahn and Barsky. Chemistry of Pernicious Anemia, Arch Int Med **23**: 334 (March) 1919.

10 Gettler and Lindeman. Blood Chemistry of Pernicious Anemia, Arch Int Med **26** 453 (Oct) 1920.

urine of four there were a few cylindroids. In addition, six patients who had degeneration of the spinal cord with cystitis or cystopyelitis, had pyuria and gave a positive reaction to the test for albumin. The urine of each patient was examined a number of times, but it is possible that had we examined it more often, the number of cases in which albumin and cylindroids were present would have been greater. The main point, however, is that albuminuria was always a transitory phenomena, and that there was only a slight trace of albumin.

As a rule, the thiosulphate test was made with the water test. The results are summed up in table 8.

If the normal limit excretion of thiosulphate is placed at 20 per cent, it will be seen that the excretion usually is normal. Seventeen determinations were slightly under this limit. In four of these, either a little of the thiosulphate was not injected into the vein, or the urine was voided three hours instead of four hours after the injection, making it impossible to complete the titring. It is possible that these four cases

TABLE 8—*Results of Thiosulphate Test with Water Test*

Thiosulphate excretion percentage	>25	25-20	20-15	15-10	<10
Number of patients	34	32	17	3	2

TABLE 9—*Blood Urea Determinations*

Blood urea in mg, percentage	<30	30-40	40-50	50-60	>60
Number of patients	34	25	21	1	5

would be above the 20 per cent limit. The remainder, as a rule between 18 and 19 per cent, are divided among normal determinations made on the same patient. There were five determinations under 15 per cent. Four of these were made in two cases. Both of the patients had degeneration of the spinal cord with sphincteric disorder and pyuria. Judged by the thiosulphate test, we concluded that in uncomplicated cases of pernicious anemia there is only a doubtful or insignificant decrease in the function of the kidneys.

Next, the blood urea must be considered. The eighty-six determinations are summed up in table 9. Twenty-one of the determinations were at the maximum of the normal limit. It is doubtful, however, whether this is an indication of a pathologic condition. Six of the determinations were beyond the maximum of the normal limit. The tests were made on the same patient, a man with hydrops. Macroscopic and microscopic examination of sections showed fibrous changes in the kidneys. It is worthy of note that in this case there was either no decrease in the thiosulphate excretion or a doubtful decrease, a circumstance that we cannot explain. We also determined the blood urea

in four cases in which the water test or thiosulphate test had not been performed. The first patient had abnormally high determinations, 83 and 73 mg per hundred cubic centimeters, incontinence of urine and pyuria. Macroscopic and microscopic examination of sections of the kidneys showed moderately pronounced fibrous changes. The last patient also had an abnormal determination, 66 mg per hundred cubic centimeters the day before death.

Finally, the blood pressure must be considered. As a rule, the determinations were low. In two instances, there was hypertension. Consequently, it can be considered that the blood pressure is usually low.

In summary. The tests show that generally there is not a noticeable kidney insufficiency, but that, as a rule, the function of the kidneys is good. It would seem unusual if nephropathy could be a determining factor in the origin of edema or the reduced excretion of water. Furthermore, Krogh,¹¹ Hagedorn and Rasmussen and Rehberg¹² have pointed out that typical nephrotic edema accompanies albuminuria, as the blood's colloid osmotic pressure is lowered by the protein loss because the small and more osmotic active protein molecules preferably are eliminated through the kidneys. A large protein loss of this kind is never observed in pernicious anemia.

Hemoglobin Content—The next question is, how great is the significance of the anemia itself, i.e., the low hemoglobin content in the production of symptoms? Essen and Poiges⁵ expressed the opinion that the kidneys, as far as the excretion of water is concerned, adapt themselves to the hemoglobin insufficiency by excreting an isotonic urine.

Our data show that edema and reduced excretion of water do not always occur when the hemoglobin content is low. Of course, both the phenomena are present during relapses and disappear during the remissions, but in many instances, there is a noteworthy incongruity. We often found a satisfactory four hour excretion of water when the amount of hemoglobin was less than 50 per cent, on the other hand, we never found a reduced excretion, when the hemoglobin content was more than 50 per cent.

To be able to determine whether the low hemoglobin content causes these symptoms, we used the water test in cases of posthemorrhagic anemia. We chose this type because in other types of anemia (leukemia, cancer, etc.) a toxic factor may be present which could complicate the experiment. Unfortunately, we had only twelve cases of posthemorrhagic anemia at our disposal for the experiment. None of the patients had edema and eleven (table 10) had a normal excretion of

11 Krogh. *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1922.

12 Hagedorn, Rasmussen and Rehberg, cited in Krogh (footnote 11).

water in four hours with a pronounced change between the greatest dilution and the greatest concentration. These observations do not indicate that the low hemoglobin content is of great significance as a cause of edema and reduction in the excretion of water.

Osmotic Pressure in the Plasma—Finally, we turned our attention to the plasma colloids and the colloid osmotic pressure in the plasma to determine whether a lowered amount of total protein and a lowered colloid osmotic pressure in the plasma could cause the edema and reduction in the excretion of water. Jaksch¹³ and Grawitz¹⁴ reported the occurrence of a small amount of total protein in the plasma. Erben¹⁵ reported one case in which there was 5.2 per cent total protein in the plasma, 4.2 per cent albumin and 1 per cent globulin with 15 per cent hemoglobin. Kahn and Barsky⁹ found a small amount of total protein in the plasma in three cases of pernicious anemia. Gettler and Linde-

TABLE 10—*Data on Water Excretion in Twelve Cases of Posthemorrhagic Anemia*

Diagnosis	Hemo- globin Percentage	Four Hour Excretion	Lowest Specific Gravity	Highest Specific Gravity
Melena	34	885	1.005	1.019
Anemia following abortion	57	994	1.004	1.026
Melena	44	1,070	1.003	1.027
Anemia following abortion	54	1,296	1.003	1.024
Hematemesis	34	715	1.008	1.025
Anemia following abortion	40	1,143	1.007	1.025
Melena	40	537	1.007	1.029
Melena	45	1,085	1.008	1.029
Anemia following abortion	55	710	1.004	1.022
Anemia following extraction of teeth	50	1,315	1.001	1.029
Melena	35	760	1.005	1.025

man¹⁰ reported the cases of thirty-two patients who had pernicious anemia and found that the refraction determinations in three fourths of them showed that the serum was below normal, and in some they found that the amount of total protein was smaller than in cases of severe nephrosis with edema. This decrease at times was from 40 to 50 per cent below the normal determinations. The specific gravity was proportionately lowered, so that 80 per cent of the determinations were below normal. Essen and Porges⁵ also found low refraction. Naegeli,¹⁶ however, reported the opposite. In his textbook, he said "Das Serum-eiweiss ist meist in ungefahr normaler Menge (7-8% Eiweiss) vorhanden, wie ich durch hunderte von refraktometrischen Untersuchungen ersehen habe. Eine Hydrämie besteht also im allgemeinen nicht. Erst bei

13 Von Jaksch. *Ztschr f klin Med* 23 186, 1892

14 Grawitz. *Berl klin Wchnschr* 35 704, 1898, *Klinische Pathologie des Blutes*, Leipzig, 1911, p. 435

15 Erben. *Ztschr f klin Med* 40 266, 1900

16 Naegeli. *Blutkrankheiten und Blutdiagnostik*, Berlin, 1923, p. 312

akuter Verschlechterung sinkt der Eiweissgehalt. Bleibt jedoch der Patient längere Zeit auf dem niedrigen Hb-wert, so stellt sich auch der Eiweissgehalt wieder auf die Norm ein. Die Globuline stehen in der Mehrzahl der Fälle an der oberen Grenze der Norm (um 40%), zeigen in einzelnen Beobachtungen aber auffällig niedrige Werte." (The protein value of the serum is generally about normal [from 7 to 8 per cent albumin], as I have seen in hundreds of refraction tests. Hence hydremia is not usually present. Only in association with an acute exacerbation does the protein content become lower. If, however, the hemoglobin value is low for some time, the protein content again becomes normal. The globulin content in the majority of cases is at the highest normal limit [about 40 per cent], but in rare cases unusually low values are seen.)

The fibrinogen has been given much study by Drinker and Hurwitz.¹⁷ They found a few patients with a normal amount in the plasma. Rusznyak, Barat and Kurthy¹⁸ found a high fibrinogen content with normal albumin and globulin determinations in some cases, and H. C. Gram,¹⁹ who made an exhaustive study of the subject, found a pronounced tendency toward low determinations.

Of the foregoing research work, Gettler's and Lindeman's¹⁰ is the most comprehensive. According to their data, a lower amount of total protein is to be expected in severe cases.

In determining the pathogenesis of edema, however, it is of the greatest importance and interest to know whether there is lowered colloid osmotic pressure in the blood. Positive proof of this was obtained in only one case, reported by Mayrs,²⁰ who found a colloid osmotic pressure of 264 mm. of water in the serum, a total protein amount of 6.0375 per cent and a colloid osmotic pressure of 43.7 per gram of albumin. There was no edema, and there is no mention of the percentage of hemoglobin. His normal determinations for the foregoing factors were 402, 7.875 and 51, respectively.

We determined the amount of total protein and the colloid osmotic pressure in the serum of eleven patients with pernicious anemia, and in one patient with anemia caused by pregnancy and resembling pernicious anemia (table 11).

We used Pulfrich's refractometer for the refraction in determining the total protein in the serum. The normal determinations as given by Reiss²¹ vary from 7 to 9 per cent, those of Naegeli¹⁶ from 7 to 9.1 per

17 Drinker and Hurwitz. The Factors of Coagulation in Primary Pernicious Anemia, *Arch. Int. Med.* **15** 733 (May) 1915.

18 Rusznyak, Barat and Kurthy. *Ztschr. f. klin. Med.* **98** 337, 1924.

19 Gram, H. C. *Disputats*, Copenhagen, 1921, p. 89.

20 Mayrs. *Quart. J. Med.* **19** 273, 1926.

21 Reiss. *Verhandl. d. Versamml. deutsch. Naturr. u. Aerzte*, 1904, p. 36.

TABLE 11—Eleven Patients with Pernicious Anemia and One with Anemia of Pregnancy

No	Date	Name	Hemo globin Age %	Edema	Water Excretion			Serum Protein Percentage	Colloid Osmotic Pressure in Mm of Water	Colloid Osmotic Pressure in Mm of Water	Remarks
					Four Hours Excretion	Highest Specific Gravity	Lowest Specific Gravity				
1	10/23/26	Mr N Son	58 23	Slight edema of the face, moderate edema of the lumbar region, slight edema of hands and legs							
2	11/18/26	Mr J M Mak	53 51	-				5.94	324.0	54.4	
	12/11/26		50	-				5.90	285.0	48.3	Blood transfusion 3 weeks previous
3	11/18/26	Mrs R Ko	71 86	Edema of the lumbar region occult edema	360	1.016	1.012	7.31	289.0	39.2	
	3/15/27		40	Slight edema of the lumbar region	181	1.017	1.006	6.98	285.0	40.8	
4	11/18/26	Mrs N Gar	72 57	-				6.98	280.0	40.1	
	4/28/27		42	Slight edema of the lumbar region, minimal occult edema	205	1.019	1.015	6.51	263.5	40.5	
5	3/15/27	Mrs B Gch	59	Trace of edema of the legs, occult edema	820	1.024	1.006	6.98	310.0	44.4	
	7/28/27		67	Slight edema of the lumbar region, slight edema of the legs, occult edema	565	1.020	1.006	6.91	321.5	46.5	Spinal degeneration
6	3/30/27	Mrs L A Jen	72 50	Slight edema of the lumbar region, trace of occult edema	660	1.020	1.007	7.20	299.0	41.6	
	4/28/27		43	Edema of the lumbar region, slight edema of the legs, occult edema	310	1.015	1.010	5.90	217.0	42.0	
7	4/28/27	Mrs E A Pet	44 15	Edema of the lumbar region, marked edema of the legs				5.70	248.0	43.5	
8	4/28/27	Miss E Hull	48 50	Trace of edema of the lumbar region, trace of edema of the legs, occult edema	530	1.021	1.007	7.12	284.0	39.9	
9	4/28/27	Mrs K L Tho	35 32	Edema of the face, edema of the lumbar region, edema of the legs	175	1.017	1.012	5.90	279.0	47.2	Blood transfusion 1 week previous
10	5/4/27	Mr O Pet	50 35	Trace of occult edema				5.90	298.0	50.5	Blood transfusion 1 week previous
11	5/4/27	Mr J P Ro	59 55	-				6.91	338.5	49.0	
12	3/8/27	Mrs M Pet	40 11	Visible edema of the face, marked edema of the lumbar region, moderate edema of the legs				5.90	253.0	42.9	Anemia of pregnancy

cent, while in a small number we found that it varied from 6.98 to 8.28 per cent. We determined the serum's colloid osmotic pressure with Krogh's osmometer. The determinations were made under Professor Krogh's direction at the Animal Physiological Laboratory. None of the patients had any indication of heart disease, there was no albuminuria nor increased blood pressure.

In looking first at the total protein in the serum, conformity with the foregoing results will be seen, as there is a lowered amount of total protein. A proportionately lower amount of protein was found in other patients with pernicious anemia. The decrease was pronounced, but not as extreme as in some nephrotic patients.

The colloid osmotic pressure of the serum is also lower. Our normal determinations varied from 401 to 325 mm. of water with an average of 362, and in patients with pernicious anemia, from 324 to 248. This decrease is moderate, as we did not find the determinations as low as in patients with nephrosis, who in severe cases have a colloid osmotic pressure as low as 80 (Iversen and Nakazawa²²).

Finally, in the last column is the colloid osmotic pressure per cent total protein. Here our normal determinations varied from 54 to 44, with 47.4 as an average, not differing from the pressure found in cases of pernicious anemia, this makes it evident that the lowering of the colloid osmotic pressure is proportional to the lowering of the amount of protein, or that this decrease is dependent on the quantitative and not on the qualitative changes in the plasma colloids. In other words, the reduction in protein affects the larger molecular and the smaller molecular plasma colloids to the same extent.

There is a decided difference in this respect in nephrotic patients, whose colloid osmotic pressure according to the percentage of albumin is lowered because the smaller molecular plasma colloids lost in the kidneys cause a relative increase of the larger molecular plasma colloids in the blood.

The question now is whether this lowered amount of total protein and the moderate decrease in the colloid osmotic pressure can be the source of the edema and the reduction in the excretion of water in pernicious anemia.

In nephrotic patients, we found that the critical zone was between 270 and 240 mm. of water. In this zone, the colloid osmotic pressure has a tendency to be the same or lower than the hydrostatic pressure in the capillaries. Some of our determinations in pernicious anemia are in this critical zone. This justifies us in believing that the low amount of protein and the low colloid osmotic pressure in the blood may be a contributing factor in the cause of edema in pernicious anemia,

22 Iversen and Nakazawa. *Biochem Ztschr* 191: 307, 1927.

and that in some cases it possibly is the dominating influence. Unfortunately, we have not had occasion to examine patients with the greatly pronounced edema occasionally found in extreme cases of pernicious anemia, but it is probable that in such cases a great reduction in the amount of protein and in the colloid osmotic pressure would be found.

There is reason to believe, however, that there is still one factor, maybe more, which is instrumental in the pathogenesis of edema and the reduction in the excretion of water. This seems to be true because there is no consistent parallelism between the amount of edema and the reduction in the excretion of water on the one hand, and the lowering of the colloid osmotic pressure on the other, one may find pronounced edema with a colloid osmotic pressure well above the critical zone. It seems to be true also because there is one fact not yet explained, namely, in posthemorrhagic anemia there is no edema or reduction in

TABLE 12—*Data on Colloid Osmotic Pressure in Three Patients with Posthemorrhagic Anemia*

No	Date	Name	Age	Hemo- globin Percent	Edema	Serum Protein Per- centage	Colloid Osmotic Pressure in Mm Water	Colloid Osmotic Pressure per Gm Protein in Mm Water	Remarks
1	10/28/16	Mr T G	34	59	—	6.46	272	42.2	Melena
2	11/15/26	Mr H P P	55	45	—	5.90	250	42.4	Melena
	12/6/26			40	—	5.68	264	46.5	Melena
	12/18/26			40	—	6.12	277	45.2	Melena
3	12/1/26	Mr O A.	27	35	—	6.34	277	43.6	Melena
	12/8/26			46	—	6.55	318	48.6	Melena

the excretion of water in most instances. Table 10 shows that there was no indication of edema or a reduction in the excretion of water among the patients with posthemorrhagic anemia. In some cases of the same type and intensity examined (table 12), it was observed that the colloid osmotic pressure was lowered and remained at the same level as in pernicious anemia. This point requires more study, but our research indicates that there may be some other factor.

This factor may possibly be weakness of the heart with the consequent increase of hydrostatic pressure in the capillaries. Or there is a possibility that in pernicious anemia during the severe periods, there may be a metamorphosis in the capillary walls and an increased permeability for the plasma colloids.

From one patient we were fortunate enough to obtain about 2 cc of edematous fluid, which on examination, was found to contain 1.1 per cent of total protein, the colloid osmotic activity however, was not determined. This is rather a large protein content, but in using such small amounts of edematous fluid mistakes undoubtedly may occur.

through mechanical injury to the capillaries. It is perhaps worthy of mention that Hess and Muller,²³ in experiments with anemia caused by blood poisons, pyrodine and toluyldiamine, found edema in the experimental animals, and that the edematous fluid from the pleurae of these animals showed a high protein content (up to 6 per cent) which the authors think was due to a toxic injury and increased permeability of the endotheliums.

SUMMARY

1 In pernicious anemia, edema frequently occurs, and the water test often shows a reduction in the excretion of water.

2 These symptoms are present during a relapse and disappear during a remission.

3 It does not seem probable that the symptoms are caused by impairment of the function of the kidneys or by the anemic condition, the low amount of hemoglobin.

4 In many instances a decrease in the total protein with a lowering of the colloid osmotic pressure in the plasma was found.

5 The lowered colloid osmotic pressure often occurs in the critical zone of the origin of the edema, and may therefore be a contributing cause in the production of edema and probably as well of the reduction in the excretion of water in pernicious anemia. One or more additional factors must also be present, however, possibly dilatation of the heart or an increased permeability of the capillary walls.

23 Hess and Muller. *Wien klin Wchnschr* 27 121, 1914.

LORDOSIS AS A CAUSE OF POSTURAL ALBUMINURIA *

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In the course of a study of various types of benign albuminuria, we have had an opportunity to study thoroughly the so-called postural albuminuria, in which albuminuria becomes manifest in certain persons if they assume the upright position and disappears if they assume the recumbent position. This type of benign albuminuria is also spoken of as orthostatic or orthotic albuminuria.

Concerning this condition, there is still much controversy regarding the factors of its production and causation. Maxon,¹ who gave the earliest description of the condition, called attention to the fact that the albuminuria was apparently not associated with evidence of renal disease. He distinguished an albuminuria of adolescence with a fairly permanent showing of albumin in the urine and a remittent type in which the albumin completely disappeared from the urine when the subject was recumbent and reappeared after assumption of the erect posture. Pavy² reported a similar group of cases. Stirling³ first emphasized the importance of posture and its definite connection with the appearance and disappearance of the albumin in the urine. Heubner⁴ suggested the term "orthotic" and Tissier⁵ the term "orthostatic."

The effect of exaggerated lordosis as a factor in the development of postural albuminuria was not stressed until Jehle⁶ published his exhaustive study on this condition. He was so impressed with the connection between the two that he suggested the term "lordotic albuminuria." Nassau,⁷ however, pointed out that there were two distinct types of postural albuminuria, a type occurring without any lordosis and a type occurring in connection with exaggerated lordosis.

* From the University of Illinois College of Medicine and the Mount Sinai Hospital.

1 Maxon, W. Guy's Hosp Rep **23** 233, 1878.

2 Pavy, F W. Brit M J **2** 789, 1885.

3 Stirling, A W. Lancet **2** 1157, 1887.

4 Heubner, O. Ueber chronische Nephritis und Albuminuria im Kindesalter, Berlin, A Hirschwald, 1897.

5 Tissier, H. Semaine med **19** 245, 1899.

6 Jehle, B. Die lordotische Albuminuria, Berlin, Julius Springer, 1914.

7 Nassau, E. Ztschr f Kinderh **33** 158 (Aug) 1922.

Various theories have been advanced as to the cause of postural albuminuria. Erlanger and Hooker⁸ believed that diminished pulse pressure was the cause and that the amount of albumin excreted varied inversely to the magnitude of pulse pressure. Mason and Erickson⁹, Bass and Wessler¹⁰ came to similar conclusions. Tissier² advanced the theory that the developmental defects of the glomeruli, with consequent increased permeability of the kidney, were the responsible factor. Jehle⁶ believed that mechanical interference with the renal circulation, such as is possible through the effect of marked lordosis, was the sole

Result of Daily Urinalyses in Twenty-Five Cases of Lordosis Over a Period of Six Months

Case	Age	Sex	Type of Deformity	Deformity Due to	Urinalysis			Microscopic
					Albumin	A	M P M	
1	14	M	Lordosis, scoliosis	Poliomyelitis	0	0	0	All negative
2	6	F	Lordosis, scoliosis	Poliomyelitis	0	0	0	All negative
3	6	F	Lordosis	Congenital spastic deformity	0	0	0	All negative
4	7	F	Lordosis	Poliomyelitis	0	0	0	All negative
5	7	M	Lordosis, tilting of pelvis	Rickets	0	—	—	All negative
6	14	F	Lordosis	Poliomyelitis	0	0	0	All negative
7	8	M	Lordosis, pelvic deformity	Poliomyelitis	0	0	0	All negative
8	9	M	Lordosis	Poliomyelitis	0	0	0	All negative
9	11	F	Lordosis	Poliomyelitis	0	0	0	All negative
10	12	F	Lordosis	Poliomyelitis	0	—	—	All negative
11	12	F	Lordosis, scoliosis	Poliomyelitis	0	0	0	All negative
12	11	M	Lordosis	Poliomyelitis	Trace	—	—	All negative
13	16	F	Kyphoscoliosis, lordosis	Rickets musculatrophy	Inconstant orthostatic albuminuria	0	0	All negative
14	11	F	Lordosis	Spastic paralysis	0	0	0	All negative
15	8	M	Scoliosis, lordosis	Poliomyelitis	0	0	0	All negative
16	19	F	Lordosis, pelvic deformity	Poliomyelitis	0	0	0	All negative
17	18	F	Lordosis	Poliomyelitis	0	0	0	All negative
18	15	F	Lordosis	Poliomyelitis	0	—	—	All negative
19	9	M	Scoliosis, lordosis	Rickets	0	0	0	All negative
20	8	F	Scoliosis, lordosis	Poliomyelitis	0	0	0	All negative
21	6	F	Lordosis	Poliomyelitis	Inconstant albuminuria	0	0	All negative
22	11	M	Lordosis	Spastic paralysis	0	0	0	All negative
23	7	F	Lordosis	Poliomyelitis	0	0	0	All negative
24	14	M	Lordosis	Poliomyelitis	0	0	0	All negative
25	12	M	Lordosis, scoliosis	Poliomyelitis	0	0	0	All negative

cause. Acute renal venous stasis ensues with retardation of venous circulation. Owing to anatomic peculiarities, this stasis is more pronounced on the left side than on the right side.

However, Goetsky's¹¹ careful observations, confirmed since by many observers, indicated that as a cause, exaggerated lordosis is probably

8 Erlanger, J., and Hooker, D. R. Johns Hopkins Hosp Rep **12** 145, 1904

9 Mason, E. H., and Erickson, R. J. Am J M Sc **156** 64, 1918

10 Bass, M. H., and Wessler, Harry. A Study of the Blood Pressure in Children Showing Orthostatic Albuminuria, Arch Int Med **13** 39 (Jan.) 1914

11 Goetsky, F. K. H. Zur Kenntnis der orthotischen Albuminuria, Diss. Berlin, August, 1910

unimportant Extended series of cases in which lordosis was pronounced, did not show albuminuria and, again, cases in which lordosis was not present, showed a large amount of albumin on change of posture

In our study of postural albuminuria, we had frequently found it difficult to determine, to our satisfaction, whether the orthostatic albuminuria was due definitely to a lordotic condition or to some other factors Since there is no way of determining with certainty what degree of malposture constitutes a deviation from the normal, we decided to select for our study, cases of unusually pronounced lordotic deformity

We therefore selected a group of twenty-five crippled children and young adults In nineteen of this group, the deformity was due to a residual paralysis of poliomyelitis, three children had had severe rickets in infancy, in three others, the deformity was the result of a congenital, spastic paralysis The types of deformities were those of simple lordosis and of lordosis associated with various degrees of scoliosis of the dorsal and lumbar spine

The patients were observed for six months All urinalyses were made on morning and afternoon specimens The mothers were instructed to collect the specimens of urine before the children got out of their beds Only those cases in which microscopic observations in the routine urinalyses were persistently negative were included in this group The urine was alkalinized in the cases of positive albuminuria and the effect on the excretion of albumin studied In two cases of persistent orthostatic albuminuria, the plasma proteins (fibrin, globulin, albumin), amino-acids and urea nitrogen were determined

COMMENT AND CONCLUSION

Contrary to our expectation, out of this group of twenty-five definitely lordotic children only three showed a persistent tendency to the orthostatic type of albuminuria This, we find, is not higher, proportionally, than in other groups of postural albuminuria without definite lordosis Three others showed the tendency inconstantly Removal of orthopedic appliances was followed by no observable change in the excretion of albumin Alkalinization of urine did not have any particular effect on the excretion of albumin The blood chemistry did not show any essential deviation from the normal, which agrees with the observations of Schlutz and Swanson¹²

As a result of our observations, we believe that exaggerated lordosis is an unimportant factor in the production of orthostatic albuminuria

12 Schlutz, M F, and Swanson, W W The Plasma Protein in Postural Albuminuria, *J A M A* **87** 1193 (Oct 9) 1926

THE DEXTROSE-TOLERANCE TEST

ITS USE IN THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS^{*}

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When there is a disturbance in the functioning of an organ, appearing either as hyperfunction or hypofunction, it is desirable in most instances to be able to determine the degree of derangement. In diseases of the thyroid, for instance, the basal metabolism can be calculated with mathematical exactness, the state of functional activity of that organ can be determined. In heart disease, however, one must be content with a classification such as that proposed by the New York Society for the Study of Cardiac Diseases. For other organs, tests have been devised, some of which accurately and some inaccurately portray the functional activity of the organ. This paper is devoted to a study of some of the methods used to determine the severity of diabetes mellitus.

Joslin,¹ in his textbook on "Treatment of Diabetes Mellitus," suggests the following classification: (a) severe cases—those in which the patients are able to metabolize from 0 to 10 Gm of dextrose daily, (b) moderate cases—those in which they are able to metabolize from 11 to 50 Gm and (c) mild cases—those in which they are able to metabolize more than 50 Gm. By dextrose is probably meant the dextrose value of all foods metabolized. All of the carbohydrates may be estimated as convertible wholly into dextrose. Fifty-eight per cent by weight of protein is converted into sugar, as has been determined by Lusk from studies on phlorizinized dogs. According to Woodyatt,² the glycerin fraction of fat may be considered as dextrose and is equal to one-tenth by weight of the fat. Macleod³ considers the question of dextrogenesis from fat as not settled. The dextrose value of foods may be tersely expressed in the following formula:

$$D = 1C + 58P + 1F$$

Another term which should be defined at this point is "dextrose balance."

* From the Department of Pathology and the Diabetic Clinic of the Jewish Hospital, Brooklyn, N Y.

1 Joslin, E P. Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p 483.

2 Woodyatt, R T. Objects and Methods of Diet Adjustment in Diabetes Mellitus, Arch Int Med 28 125 (Aug) 1921.

3 Macleod, J J R. Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Company, 1926, p 123.

By this is meant the difference between the amount of carbohydrate ingested and the amount of dextrose excreted in the urine. It is evident that if the "dextrose balance" is to have any significance, the patient must be in nitrogenous and caloric equilibrium. Even then one is uncertain as to whether only the food ingested was metabolized.

To Woodyatt² foods are of significance in diabetes mellitus only so far as they give rise to dextrose or fatty acids. He attributes to the internal secretion of the pancreas, so far as metabolism is concerned, but one function—the control of the metabolism of carbohydrates.

He illustrates his conception by a study of one case (table 1). The patient was put successively on diets 1, 2 and 3. On diet 1, which had a dextrose value of 159, he excreted 50 Gm of dextrose. This gave a dextrose balance of 109 Gm. Diets 2 and 3 were entirely

TABLE 1—*The Dextrose Balance Produced with Different Test Diets in a Case of Diabetes Mellitus, Observed by Woodyatt*

Diet	Carbo hydrate	Protein	Fat	Total Calories	Dextrose Value	Dextrose Excreted	Dextrose Balance
1	92	103	70	1,436	159	50	109
2	84	11	162	1,836	116	0	116
3	28	11b	160	2,054	112	0	112

TABLE 2—*Wilder's Observations of the Dextrose Balances in a Case of Diabetes Mellitus Under Influence of Test Diets*

Diet	Carbo hydrate	Protein	Fat	Units of Insulin	Dextrose Value	Calories	Dextrose Excreted	Dextrose Balance	Blood Sugar
1	112	45	142	15	152	1,956	9.5	142.5	0.22
2	41	159	118	15	145	1,907	47	93	0.23

different from diet 1, in respect to both total number of calories and the proportions of the various foods. Diets 2 and 3 did not cause glycosuria. This gave dextrose balances of 116 and 112, respectively, which were almost equal to the dextrose balance produced with diet 1. Woodyatt concludes that dextrose is the sole food of importance in diabetes mellitus, and that it matters little whether the dextrose is derived from proteins, carbohydrates or fats. If we are to accept his conception, then the classification of Joslin, mentioned previously, is sound. One strong criticism may be offered—the patient was not in either caloric or nitrogenous equilibrium. Under these circumstances little significance could be attached to the dextrose balances.

Wilder and his collaborators,⁴ from the study of a case (table 2), reach conclusions that are completely at variance with those of Woodyatt.

4 Wilder, R. M., Boothby, W. M., Baborka, C. J., Kitchen, H. D., and Adams, S. F. Clinical Observations on Insulin, *J. Metab. Research* 2:701, 1922.

Diets 1 and 2 were isocaloric and isosaccharin, in diet 1, most of the dextrose was derived from carbohydrates, and in diet 2 from proteins. With each diet the patient received 15 units of insulin. On diet 1, he excreted 9.5 Gm of dextrose, giving a dextrose balance of 142.5 Gm. On diet 2, he excreted 47 Gm, giving a dextrose balance of 98 Gm. It is not within the scope of this paper to discuss the reasons for these results. They definitely contradict the conclusions of Woodyatt.

Of great importance is the work of Allen⁵ on the influence of fat and total number of calories on diabetes and on the requirement of insulin. He has shown that an increase in the amount of fat in the diet raises the insulin requirement out of all proportion to the amount of sugar derived from the fat. An increase in the total number of calories has a similar effect. He concludes that insulin is concerned with the metabolism of all foods—carbohydrate, protein and fat—

TABLE 3—Comparison of Diets Used by Joslin with Those Used by Newburgh and Marsh

(a) Joslin's Diets	Carbohydrate	Protein	Fat	Calories
Test diet 1	181	46	44	1,304
2	101	35	43	931
3	66	24	37	693
4	34	15	30	466
Maintenance diet no. 12	159	84	135	2,187
(b) Newburgh and Marsh Diets	14	10	90	900
	15-20	28	140	1,400
	25-30	30-40	170	1,800

and with anabolic as well as catabolic processes. He stresses also the paradoxical so-called "law of dextrose," namely, that the increment in the dosage of dextrose is always greater than the increment of excretion. The test and maintenance diets employed by Joslin⁶ are utterly different in the proportion of the various foods from those utilized by Newburgh and Marsh⁷ (table 3).

It is evident that a classification of diabetes which takes into account only the dextrose of the diet of a patient who is on a mixed diet is fallacious.

Joslin¹ proposes another classification, which is more in conformity with the work of Wilder⁴ and Allen⁵. It is based on the requirement of insulin when the patient is ingesting 1 Gm of carbohydrate, 1 Gm of protein and 2 Gm of fat per kilogram of body weight. If insulin

5 Allen, F. M. Influence of Fat and Total Calories on Diabetes and the Insulin Requirement, *J. Metab. Research* 3: 61, 1923.

6 Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p. 493.

7 Newburgh and Marsh, quoted by Joslin (footnote 1, p. 527).

is not required, the case may be considered mild, if less than 30 units are required, moderate, and if more than 30 units, severe. This classification is sound, although the low diet would cause a negative caloric balance. The objection to it is that the diet is fixed. The degree of mildness is not determined. Another consideration is the method of administration of insulin, divided doses are far more potent than a single large dose containing the same number of units. The dextrose equivalent of insulin diminishes with increase in dosage.

It may be assumed that both methods of determining the tolerance take into account the amount of glycosuria. A criticism that may be offered is that they do not take into consideration the marked differences in renal threshold in diabetic patients. If, for example, two persons with diabetes who have different renal thresholds, but whose pancreases are equivalent so far as functional activity is concerned are put on the same diet, and this diet is in excess of their tolerance, the one with the lower renal threshold will excrete far more dextrose and will be considered to have the more severe diabetes. Although the functional activity of the pancreas is the same in each, the one with the higher threshold appears to have the milder case, because he is given more time in which to metabolize the food. The high renal threshold acts as a compensating mechanism. This phase of the subject will be amplified later.

THE DEXTROSE-TOLERANCE TEST AS A METHOD FOR THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS

A dextrose-tolerance test was made on seventeen patients suffering from diabetes of varying degrees of severity. Each patient after fasting fourteen hours received 100 Gm of dextrose. From each of these patients four blood specimens were taken—one, at the "fasting level," immediately before ingestion, and three at forty-five minutes, two hours, and three hours after ingestion, respectively. The sugar content of the blood was determined by the Kramer-Gittelman method⁸; blood for this test is obtained by pricking the finger tip. It was shown by Foster⁹ that the content of sugar in such blood is identical with that in blood derived from the radial artery, in other words, blood from the finger tip may be considered arterial blood. In the state of fasting, the blood sugar concentration of venous is equal to that of arterial blood, after the ingestion of dextrose, however, the sugar concentration of venous becomes less than that of arterial

8 Kramer, B, and Gittelman, I F. Technic for Quantitative Estimation of Glucose in Small Amounts of Blood, *J A M A* **81** 1171 (Oct 6) 1923

9 Foster, G L. Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, *J Biol Chem* **55** 291 (Feb) 1923

blood, supposedly because the muscle cells take up dextrose. Most investigators have found the difference to be less in diabetic patients. This fact is not of importance so far as this work is concerned.

The curves portraying dextrose tolerance are recorded in table 4. The various features of the test will be discussed separately.

Dosage—The ideal method of administration would be the timed intravenous injections as proposed by Sansum and Woodyatt.¹⁰ They showed that in man the injection of as much as 0.85 Gm. of dextrose per kilogram of body weight per hour did not cause glycosuria. For obvious reasons, their method is not feasible for ordinary purposes. The dosage chosen in this experiment was 100 Gm. of dextrose given in the form of a 50 per cent solution. This is the amount also employed by

TABLE 4—*Sugar Concentration of Blood and Excretion of Dextrose in Diabetes in Tests Made Periodically Following Administration of 100 Gm. of Dextrose*

Case	Blood Sugar Concentrations				Dextrose Excreted*
	Fasting Level, Before Ingestion	45 Minutes After Ingestion	2 Hours After Ingestion	3 Hours After Ingestion	
1	172	206	333	337	9.6
2	173	360	326	297	1.0
3	177	322	257	252	10.3
4	181	296	274	199	8.0
5	184	261	270	248	18.0
6	186	314	249	186	13.6
7	207	331	317	333	13.4
8	209	309	255	217	2.6
9	218	357	401	292	12.5
10	222	355	283	223	7.5
11	222	386	462	320	22.1
12	243	260	463	389	31.6
13	249	392	422	375	17.5
14	289	411	522	467	
15	298	355	428	295	16.2
16	305	411	410	370	
17	335	574	670	431	51.5

* Grams excreted in three hour period.

Hamman and Hirschman,¹¹ John¹² and others. Janney and Isaacson¹³ gave 1.75 Gm. of dextrose per kilogram of body weight, holding that the "dextrose load" should be proportional to the weight of the individual. Gray¹⁴ has shown that in a normal person, the maximal rise

10 Sansum, W. D., and Woodyatt, R. T. Studies on Theory of Diabetes VIII. Timed Intravenous Injections of Glucose at Lower Rates, *J. Biol. Chem.* **30**: 155 (May) 1917.

11 Hamman, L., and Hirschman, I. J. Studies in Blood Sugar, *Arch. Int. Med.* **20**: 761 (Nov.) 1917.

12 John, H. J. Glucose Tolerance Test and Its Value in Diagnosis, *J. Metab. Research* **1**: 497, 1922.

13 Janney, N. W., and Isaacson, V. I. Blood Sugar Tolerance Test, *J. A. M. A.* **70**: 1131 (April 20) 1918.

14 Gray, H. Blood Sugar Standards, Normal and Diabetic, *Arch. Int. Med.* **31**: 241 (Feb.) 1923.

in blood sugar concentration is the same for a dextrose load of 20 Gm as for one of 200 Gm. An increase in the dextrose dose administered to a diabetic person would result merely in the prolongation of the curve.

In a normal person, given 100 Gm of dextrose on a fasting stomach, the concentration of sugar in the blood proceeds as follows. The maximal increase usually occurs at the end of one-half hour and is rarely more than from 30 to 50 per cent above the concentration at fasting level, at the end of two hours, the fasting level—and many times a value even lower than that—should be regained. Glycosuria should not occur. In diabetic patients, the curve is entirely different.

Fasting Level—The average concentration of sugar in the blood of normal persons when fasting is 0.09 per cent. As a rule, it is higher in diabetic patients. Treatment may cause it to fall to normal. During the so-called inanition treatment, it may fall to a value below normal. The very high values are obtained in cases complicated by severe acidosis, especially those comatose and in which nephritis is present. Even in cases in which the fasting level is normal, the blood sugar concentration may rise to enormous values during a dextrose-tolerance test. As a rule, however, this is not the case. On inspection of table 4, it can be seen that, with some exceptions, the fasting level is proportional to the height of the curve. When one compares the fasting level with the amount of dextrose excreted in three hours, it is noticed that a definite relationship cannot be established between them.

Character of Curve—In the majority of cases of diabetes, the maximal increase in dextrose concentration occurs either one hour or two hours after ingestion. This is not due to deficiency in absorption, for it is reasonable to assume that the rate of absorption in diabetic persons does not differ from that in normal persons, and in the latter the maximal blood sugar concentration usually occurs at the end of one-half hour. The blood sugar concentration does not reach the fasting level for from four to nine hours.

Glycosuria—Hamman and Hirschman¹¹ and others find the renal threshold of normal persons to be about 170 mg of dextrose per hundred cubic centimeters of blood. Roe and Irish,¹⁵ in a study of 100 cases of diabetes, found threshold values ranging from 80 to 310. They believe that the co-existence of nephritis is the cause of the high threshold values. They also found that the threshold varies markedly in the same individual. John¹² concludes that the renal threshold for dextrose is definitely raised in many cases of diabetes, and that the more pro-

15 Roe, J. H., and Irish, D. J. Sugar Threshold in One Hundred Diabetic Cases, *J. A. M. A.* 84:1406 (May 9) 1925.

tracted and severe the case, the higher the threshold. Williams and Humphreys¹⁶ concur in this view. Macleod¹⁷ states that the toxic effect of a high content of sugar in the blood renders the kidney impermeable to it. Faber and Norgaard,¹⁸ also Hagedorn,¹⁹ occupy a unique position on this question. They do not find any relationship between the dextrose threshold and age, sex or the duration of the illness. They believe that the threshold is peculiar to each person and is immutable.

In a normal individual, the respiratory quotient during a dextrose tolerance test rises to 1, and even above 1 if there is conversion of dextrose to fat. The body suddenly flooded with dextrose concentrates on storing and oxidizing it, the metabolism of fat and protein is reduced to a minimum. It is reasonable to assume that a similar state exists in diabetic patients, that the insulin secreted by the pancreas will devote itself almost entirely to taking care of the dextrose. The obstacle which confronted one in the previous classifications, namely, that the patients were on mixed diets, has been obviated in these experiments.

I shall now consider the relationship between the amount of glycosuria and the character of the blood-sugar curve (table 4). The curve of the blood sugar concentration of case 8 is definitely higher than that of case 6, but in the latter five times as much dextrose was excreted during the three hour period. The curves for cases 13 and 15 are only slightly lower than that for case 12, but in the latter there was excretion of twice as much dextrose. The curve for case 17 is markedly higher than that for case 12, but the amount of glycosuria was the same. It can be seen that the high renal threshold causes a reduction in glycosuria. The amount of glycosuria cannot be taken as an index of the severity of diabetes.

The question now to be considered is this: To what extent may the character of the blood sugar curve—that is, the height and the length—be taken as an index of the severity of diabetes? Four possible influences on the curve must be considered: dosage, variations in absorption of dextrose, blood volume, and renal threshold.

The dose here is uniform, 100 Gm. of dextrose are given to each patient. It was stated before that Janney and Isaacson give 175 Gm.

16 Williams, J. R., and Humphreys, E. M. The Clinical Significance of Blood Sugar in Diabetes Mellitus, *Arch. Int. Med.* **23**: 546 (May) 1919.

17 Macleod, J. J. R. Recent Work on the Physiologic Pathology of Diabetes, *J. A. M. A.* **62**: 1222 (April 18) 1914.

18 Faber, K., and Norgaard, K. The Relation Between Glycosuria and Glycemia, *Acta med. Scandinav.* **53**: 666 (Jan.) 1921.

19 Hagedorn, H. C. On the Threshold Value of Glycosuria, *Acta med. Scandinav.* **53**: 672 (Jan.) 1921.

per kilogram of body weight. It must be remembered that in persons who are overweight there is much inactive tissue.

The volume of blood increases with increase in weight, but not directly, a thin person has proportionately more blood than an obese one. When the blood sugar concentration is high, 0.4 per cent, for instance, the total dextrose content of the blood of an obese individual may be considerably greater than that of a thin one.

It has been shown that the rate of absorption of dextrose varies considerably in different individuals.

The matter of variation in renal threshold has been discussed fully in foregoing paragraphs.

To what extent is the character of the blood sugar curve influenced by these variables? Cursorily, one would state that these factors influence it markedly. Gray¹⁴ and many others have tested the influence of various "dextrose loads" on the character of the blood sugar curve. Gray has summarized the work of many authors. He showed that in normal persons, although the dextrose load varied from 20 to 200 Gm, the height of the blood sugar curve was the same in each case. He found that the height of the blood sugar curves in diabetic patients with the same fasting levels was the same regardless of whether the dextrose load was 50 or 100 Gm. Small doses, down to even 10 Gm, were suggested by Hamman and Hirschman, who wrote "The general features of the diabetic sugar curve are faithfully reproduced by patients receiving, on account of the severity of the disease, smaller amounts of glucose." Apparently, the effect of the large doses is to prolong the curve. These observations, it appears to me, definitely reduce the variables mentioned to negligible factors.

A most important function of the pancreas (insulin) is to maintain a normal blood sugar concentration. The functional activity of the pancreas may be judged by its ability to do so. The height of the blood sugar curve may tentatively be accepted as an index of the severity of the diabetes. The severity is not directly proportional to the height of the curve, for it has been shown by Allan²⁰ and others that the dextrose equivalent of insulin is greater when the dose of insulin is reduced and also when the amount of dextrose is increased.

The patients were on maintenance diets previous to the performance of the dextrose tolerance test. The test is not valid when made on diabetic patients who have fasted several days, for it has been shown that normal rabbits who have been kept from food for several days will have diabetic dextrose tolerance curves.

A question which is relevant to this subject is this: Does the administration of dextrose lead to a breaking down of tolerance? Carbo-

20 Allan, F. N. Glucose Equivalent of Insulin in Depancreated Dogs, *Am J Physiol* **67** 275 (Jan) 1924.

hydrate has always been considered the bête noire of diabetic persons. Joslin²¹ deprecates the use of dextrose-tolerance test, although he has never seen a diabetic patient injured by it. Ohler²² also argues that on theoretical grounds the giving of large quantities of dextrose is harmful. Hamman and Hirschman,²³ in the dextrose-tolerance tests performed on diabetic persons, used from 10 to 100 Gm of dextrose, depending on the severity of the case. Allen,²⁴ in his work on partially depancreatized dogs, found that excessive feeding of carbohydrates, especially when given in a readily absorptive form, such as dextrose, leads to a rapid breaking down of tolerance. He elaborates on the theory of "overstrain" of the β -cells of the islands of Langerhans, which leads to hydropic degeneration. However, there is no other animal tissue, so far as I am aware, in which structural changes similar to those observed in the islands occur as a result of overstrain. Macleod²⁵ states "It would be almost unique as an etiological factor, the only other known instance being in an experiment by Barany, in which structural changes were observed to occur in the cells of the nucleus acusticus as a result of the receipt by them of persistent sound impressions." Jensen and Carlson²⁶ agree with Macleod and state that the usual result of overstrain is marked hypertrophy, not atrophy. Wilder and his associates¹ showed that the dextrose derived from protein requires far more insulin for metabolism than do the carbohydrates. I observed for several months seven patients who had had two dextrose tolerance tests performed two days apart. None of these patients showed the slightest change in tolerance as a result of this procedure. I believe that it is innocuous.

SUMMARY AND CONCLUSIONS

Various methods for determining the severity of diabetes are discussed. Classifications which take into account only the amount of glycosuria are fallacious, for insulin is concerned with the metabolism of all foods—carbohydrates, proteins and fats. Such classifications are also vitiated by the fact that the renal threshold for dextrose is

21 Joslin, E. P. *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1923, p. 170.

22 Ohler, W. R. *Lessons to Be Learned from Repeated Glucose Tolerance Tests*, *Med Clin N Amer* **5** 1465 (March) 1922.

23 Allen, F. M. *Production and Control of Diabetes in the Dog, Effects of Carbohydrate Diets*, *J Exper Med* **31** 381 (April) 1920.

24 Macleod, J. J. R. *Carbohydrate Metabolism and Insulin*, New York, Longmans, Green and Company, 1926, p. 53.

25 Jensen, W. W., and Carlson, A. J. *Apparent Influence of Diet of Carbohydrates on Pancreas Remnant of Partially Pancreatectomized Dogs*, *Am J Physiol* **51** 423, 1920.

different for each person. A high renal threshold, which acts as a compensating mechanism, would mask a severe case.

The dextrose tolerance test as a method for determining the severity of diabetes is considered. It is shown that the amount of glycosuria occurring during the test cannot be taken as an index of severity because of differences in renal threshold in different individuals. It is shown that the height of blood sugar curve in such tests, however, may be accepted as a criterion of the gravity of diabetes.

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Book Reviews

PATHOLOGICAL PHYSIOLOGY OF INTERNAL DISEASES FUNCTIONAL PATHOLOGY
By ALBION WALTER HEWLETT Revised in memoriam by his colleagues
With 164 illustrations New York D Appleton & Company, 1928

The third edition has been prepared from the notes left by Doctor Hewlett and represents a memorial tribute to the great clinician and physiologist who died in the prime of life. There has been a complete and thorough revision of the entire volume so as to include recent developments in physiologic and clinical fields.

To the chapter on the heart are added the theory of circus movement, the use of quinidine in auricular fibrillation, the discussion of clinical ventricular fibrillation, and mention of the new work on the relation of the cervical sympathetic to angina pectoris.

The chapter on digestion includes the recent work of Ivy on the various phases of gastric secretion, Bloomfield and Keefer's method of gastric analysis and other aspects of gastro-intestinal physiology. Insulin is included in the discussion of diabetes mellitus, and the newer work on the relationship of changes in the energy metabolism to obesity is taken up. The discussion of the vitamins has been brought up to date down to vitamin E.

The chapter on the acid base equilibrium has been extensively modified and enlarged to make room for the work of the Henderson and Van Slyke schools, and is really a model chapter. The same comment applies to the chapters on respiration and carbohydrate metabolism. In the discussion of renal function, perhaps too much space is given to Schlayer's tests and insufficient mention made of the urea concentration tests as devised by Addis and others. Furthermore, renal edema is still discussed largely from Widal's point of view and not enough from the physiologic aspects of fluid exchange, including the question of the osmotic pressure of plasma proteins and other factors. It seems to the reviewer that the plasma proteins might be taken up in a chapter on renal edema rather than in a discussion of "hydremia," because the latter term itself might just as well be left out entirely in view of its misinterpretation by many.

Taken as a whole, however, this book represents probably the best of its kind not only in the English language but in any language, and is, therefore, a fitting tribute to the memory of the late Doctor Hewlett.

SYPHILIS UND INNERE MEDIZIN, III DIE SYPHILIS DES ZIRCULATIONS- UND RESPIRATION-TRAKTES UND DER INNERSEKRETORISCHEN DRUSEN SYPHILIS UND BLUTKRANKHEITEN By H. SCHLESINGER, Director of the third medical division, Allgemeine Krankenhaus, Vienna. Pp 234 Price, 18 marks Vienna Julius Springer, 1928

This volume comprises a fairly complete treatment of the many aspects of syphilis of the cardiovascular system, endocrine glands and the relation between syphilis and diseases of the blood. Syphilis of the pulmonary system and the special problems presented by coincidental syphilis and pulmonary tuberculosis are considered fully.

The more important subjects are taken up according to pathology, diagnosis, prognosis and therapy. The more uncommon conditions are aptly illustrated by the author's own cases. General syphilologic principles are interwoven more adequately than in most publications from the internist's pen.

A few American authors are quoted. The author states that antisyphilitic therapy is becoming more and more the function of the general practitioner, internist and neurologist. This is in contrast to the situation in this country, where antisyphilitic therapy has reached a higher degree of perfection, encouraging

centralization under one head, with excellent diagnostic and follow-up cooperation on the part of other specialists

The author erroneously states that original "salvarsan" is the drug of choice for therapy of cardiovascular syphilis in this country, and does not mention the extensive use, intramuscularly, of sulpharsphenamine for the purpose of avoiding vascular shock in these cases. He discusses the arsenical spirocide (acetarsone [stovarsol]) for oral administration.

It is advantageous to restrict the activities of patients with syphilitic aortitis more rigorously than suggested. It would hardly be advisable to allow an American patient to partake of dancing, swimming and physical sports, even in restricted measure.

This work fills a real need for a more or less encyclopedic treatment of these internal medical problems in the realm of syphilology.

LOCAL IMMUNIZATION By A. BESREDKA, translated by HARRY PLOTZ. Price, \$3.50. Baltimore: Williams and Wilkins Company, 1927.

This small book is divided in five chapters: Anthrax, Staphylococcus, Streptococcus Infections, Dysentery, and Typhoid Fevers, the last chapter is devoted to a discussion of theory.

The chapter on anthrax is the best of the group. The experimental evidence is most convincing. The staphylococcus is next in order of completeness. The chapters on dysentery and on typhoid are not so thoroughly treated. "Bilivaccin" pills that are used so extensively in oral vaccination are not described any place in the book. The wet dressings with filtered staphylococcus cultures or the "antivirus" (Besredka) should be of general interest as a prophylactic active immunization procedure. There are great possibilities for the use of streptococcus in this connection.

The book is well written and is easy to read. The whole theory is something new and opens up a large and almost unexplored field.

DENTAL INFECTION AND SYSTEMIC DISEASE By RUSSELL L. HADEN. Price, \$2.50. Illustrated with 63 engravings. Philadelphia: Lea & Febiger, 1928.

In this small, well illustrated volume, there is an excellent presentation of the problems of dental infection and a good description of the radiographic and clinical methods of diagnosis. Unfortunately, the author's views and his experimental work are so saturated with an uncritical enthusiasm for Rosenow's theory of "elective localization" that the book is full of misrepresentations and dogmatic statements. The attempt to diagnose metastatic infection in patients from the results of inoculation into animals of bacteria obtained from roots of teeth is almost ludicrous as it is presented in some of the case reports. One wonders why rabbits do not develop "elective localization" of bacteria in the site most frequently involved in patients—the peri-apical tissues of the teeth. The author comes back to earth and to solid clinical common sense in parts of the concluding chapter when he discusses what should be done for focal dental infection in various types of patients.

PRACTICAL GASTROSCOPY By JEAN RACHET, M.D., Paris. Authorized Translation by FRED F. IMIANITOFF, Brussels. Price, \$5.50. Pp. 148. New York: William Wood & Company, 1927.

This book is a complete survey of the subject of gastroscopy. After a brief prelude of the historical periods and the principles underlying the design of a gastroscope, the author proceeds to the gastroscopic examination, bringing out clearly its indications and contraindications. In chapter IV he presents the results obtained and shows several excellent roentgenograms. His conclusions as to the results obtained, and the future of gastroscopy are those of one well acquainted with his subject. The book can be recommended to all interested in this phase of gastro-intestinal work.

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CHANGES IN THE FUNDUS OCULI AS A DEFINITE INDEX TO ARTERIAL DISEASE

ANALYSIS OF ONE HUNDRED CASES^{*}

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It is universally recognized that marked changes of the retinal arteries are associated with changes in the organs, particularly in the kidneys. That changes in the fundus can be found in general arteriosclerosis and in interstitial nephritis in their incipency, and that such changes are synchronous with corresponding changes in the kidney and other organs, has not been sufficiently emphasized. While much has been written, the trouble has been that the ophthalmologist has not delved deeply enough into the medical aspect, and the internists are not sufficiently keen with the ophthalmoscope.

It is my contention that sclerosis of the arterioles of the kidney and brain cannot exist in the absence of a similar condition of the retinal arteries, and normal retinal vessels definitely exclude interstitial nephritis of the sclerotic type (small contracted kidney). Nephritis, or "nephrosis," such as is encountered following one of the infectious diseases, or possibly is caused by focal infection and is characterized by considerable albuminuria, may exist without arterial disease. The fundus in these cases may be normal or may sometimes show albuminuric neuroretinitis without any, or with slight, sclerotic changes in the retinal arteries. To support this theory, I have compiled a number of cardiovascular cases from the medical service of Montefiore Hospital with a study of blood pressure, blood chemistry and kidney function in relation to the appearance of the fundi.

Changes in the retinal arteries correspond to the degree of development of arterial disease in the organs and in the brain. To facilitate their recognition, I have numbered them in the order of their usual appearance, as pointed out in a previous paper.

(1) Increased light reflex. In young persons, the light falling on the arteries and veins creates a white line coursing unsteadily on top of the vessels. This is a manifestation of what is known as juvenile reflex, and is accompanied by a silvery shimmer of the retina. Older patients with normal arteries show only a slight reflex.

^{*}Read before the Section on Ophthalmology, New York Academy of Medicine, Jan 16, 1928.

^{*}From the Medical and Neurological Service of Montefiore Hospital.

(2) Reflex more marked The color and caliber of the arteries is unchanged, but there is a slight pressure effect on the veins By the latter is meant the effect on the outline of the vein as a sclerotic artery passes over it In proportion to the degree of sclerosis, the lumen of the vein is attenuated, or the vein may actually disappear for a short distance as it passes under the artery In this second degree, there is only a slight narrowing of the vein

(3) Copper wire arteries The arteries become slightly narrower than normal, somewhat uneven in caliber and decidedly paler Pressure effect on the veins is marked

(4) The same as (3) with tortuosities of the small branches of the arteries and veins, particularly in the region between the disk and the macula

(5) The same as (3) and (4), with marked tortuosities with small hemorrhages and exudates

(6) Perivasculitis, with occlusion of small branches

(7) Edema of the disk with larger exudates and hemorrhages, atrophy of the retina, with low grade pigment proliferation

Blocking of the central retinal artery is most likely to occur in arteriosclerosis of the second or third degree

Moderate sclerosis of the retinal blood vessels may be accompanied by advanced sclerosis of the choroidal blood vessels The vessels of the choroidal mosaic become pale and sharply defined Visibility of the choroid is due to atrophy of the pigment epithelium

The average blood pressure corresponding to that in (1) is normal, in (2), 150 to 160, (3), 170 to 180, (4), 190 to 200, (5), over 200

The early changes are frequently unnoticed, and the results of the examination of the fundus are called negative In the absence of changes in the retinal arteries, high blood pressure is most likely functional, and the kidney, normal

The first most important definite sign is the pressure effect on the veins This is usually accompanied by pale copper wire arteries In the presence of some pressure effect, with large arteries of good color, there is no elevation of blood pressure In examination for life insurance, a careful scrutiny of the fundi would yield the examiner considerably more information than just taking the blood pressure The latter can be temporarily reduced by a starvation diet, even the urine can be freed from a trace of albumin, but the appearance of the fundus is constant I would, for instance, consider a man, 50 years of age, with normal retinal arteries, a good risk in the absence of any surgical pathologic condition On the other hand, a patient showing change (2) in his retinal arteries would surely be a poor risk, even though normal otherwise His arteriosclerosis is apt to progress, he may develop blocking of a cerebral artery or vein or even blocking of the coronary artery This inference is drawn from the occurrence of so many cases of hemiplegia and angina without high blood pressure endocarditis or syphilis Severe attacks of cerebral apoplexy are more frequent in patients without high blood pres-

sure, and are usually unexpected. A careful examination of the fundus in these cases would disclose incipient arterial disease.

What may occur in cerebral arteries and veins can be visualized in cases of blocking of the central retinal arteries and veins. A good demonstration of what may happen was seen in a patient who came to the New York Eye and Ear Infirmary, Dr. Shine's service, with a blocking of the central artery. While his blood pressure, which was found to be 160 systolic, was being taken, he developed a hemiplegia.

Clinicians, as a rule, will distinguish between attacks of "stroke" in the presence of low blood pressure and apoplexy in the presence of high blood pressure. They ascribe the former to thrombosis of the cerebral artery or its branches, and the latter to hemorrhage caused by rupture of a cerebral artery. Patients with high blood pressure are more apt to have hemorrhage from the smaller branches of the arteries or veins, or else they may have blocking of the smaller branches, as in the presence of high blood pressure they are not likely to develop a thrombosis in the larger trunks unless the disease is far advanced, because the high blood pressure creates a strong "*vis a vigo*."

When one sees what happens in the retina as a result of thrombosis of the central vein, i. e., large hemorrhages, it seems to me that in the presence of moderate elevation of blood pressure or low blood pressure a similar accident may occur in the brain. Of course, free collateral venous circulation of the brain must be taken into consideration. A thrombosis of the central artery results in atrophy of the retina, in the brain, blocking of a cerebral artery results in softening of the brain. The extent of the disease depends on the size of the blood vessel which was blocked. It would seem logical to come to the conclusion that severe attacks of apoplexy with hemiplegia are not always caused by hemorrhage from a ruptured artery, but may be caused either by thrombosis of a large artery or vein in the absence of high blood pressure or in the presence of a rapid drop in blood pressure, such as might be caused by shock with weakened heart action. In fact, strong doubts may be entertained as to the frequency of rupture of larger branches of arteries. These conclusions are drawn merely from careful study of the behavior of the retinal arteries. I have never seen a rupture of the retinal artery, except at the terminals. Atheroma of the arterial wall, I believe, occurs only in the larger arterial trunks.

Further study of the retina disclosed that cases of peripheral arteriosclerosis, such as is found in old people, is not necessarily associated with changes in the retina. Patients with this condition may have a normal blood pressure and normal kidney function, and longevity is not affected. This observation may again be visualized in the eye, where peripheral arteriosclerosis, while not affecting the retinal blood vessels, is often marked by sclerosis of the choroidal blood vessels, with secondary

Observations in Cases of Arterial Disease

Name	Age, Sex	Diagnosis	Estimated Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg per 100 Cc	Urine	Retinal Changes
D T	63 ♂	Advanced arteriosclerosis, cardiac decompensation and insufficiency	170-180	170/100 206/100	4,650,000, hemoglobin, 85%	Urea nitrogen, 30.1, sugar, 120	Faint trace of albumin	(3), arteriosclerosis
R W	45 ♀	Diabetes, general arterio-sclerosis, cardiac hypertrophy, hemiplegia	160	162/80	4,080,000, hemoglobin, 75%	Urea nitrogen, 11.5, sugar, 337, cholesterol, 170	Sugar, negative; albumin, negative	(2)
J R	46 ♂	Hypertension, arteriosclerosis, cardiac hypertrophy and dilatation, mitral insufficiency, hydrothorax, ascites, arrhythmia	160	175/125 180/116	5,100,000, hemoglobin, 75%	Urea nitrogen, 15.1, sugar, 86	Trace of albumin	High degree of myopia, sclerosis of choroidal blood vessels, retinal blood vessels, (2)
M S	46 ♀	Hemiplegia	200+	150/140	S-----	Urea nitrogen, 32.5, sugar, 105	Albumin, 3+	(7)
A P	51 ♂	Auricular fibrillation, hypertension	160	169/126 226/128	5,210,000, hemoglobin, 95%	Urea nitrogen, 18.6, sugar, 110	Sugar, +, albumin, negative granular casts	(2)
S O	51 ♀	Chronic neuritis	Normal	126/78	4,300,000, hemoglobin, 80%	Urea nitrogen, 10.9, uric acid, 2.5, sugar, 100	Negative	High degree of myopia, (1)
S W	50 ♂	Mitral stenosis and insufficiency, general arterio-sclerosis, cardiac hypertrophy, arrhythmia	160-170	160/70		Urea nitrogen, 17.6, sugar, 121	Negative	(2), Drusen
J S	57 ♂	Mitral insufficiency, chronic nephritis?	160	162/100 190/90 160/100 206/130			Negative	(2)
N F	57 ♂	Cerebral hemorrhage, encephalomalacia, arteriosclerosis, cardiac hypertrophy and dilatation	190-200				Negative	(4)
L D	53 ♂	Obesity, syphilis, aortitis, aortic insufficiency	180	124/62		Urea nitrogen, 14.7, sugar, 118	Negative	(3)
B K	55 ♀	Diabetes, chronic nephritis, aortic dilatation and insufficiency, arteriosclerosis	200	210/80	2,330,000, hemoglobin, 40%	Urea nitrogen, 27.3- 88.9, sugar, 122-150	No albumin, but many granular casts	(5)
J S	51 ♂	Diabetes, multiple neuritis, general arteriosclerosis, one leg amputated	160	136/60 168/72	4,224,000, hemoglobin, 70%	Urea nitrogen, 17.8, sugar, 108, cholesterol, 183	Trace of albumin, otherwise negative	Arteriosclerosis, (2), diabetic retinitis
H R	47 ♀	Chronic pulmonary tuberculosis, incipient hypertension, cardiac hypertrophy	160	166/85				Right eye, very narrow arteries, as if partially occluded, macula darker than normal left eye, opacity of cornea, narrow arteries (2)
R B	57 ♀	Diabetes, hypertension, cardiac hypertrophy, cholecystitis	160	166/78		Urea nitrogen, 7.1, sugar, 192	Trace of sugar	

Y K	50	Diabetes, cerebral arterio-sclerosis, aphasia	190-200	170/94 102/86		Urea nitrogen, 16.8, sugar, 2.2, cholesterol, 111	Dextrose plus albumin, trace, a few granular casts Negative	(4)
I G	63	Coronary arteriosclerosis, general arteriosclerosis	150-160	148/82	4,060,000	Urea nitrogen, 11.9, sugar, 101	Negative	(2), coronary attacks probably caused by contraction of artery (2)
S G	64	Hypertension, cerebral thrombosis, (essential hypertension)	160	220/115	3,800,000, hemoglobin, 80%	Urea nitrogen, 31.6, sugar, 157	Negative	(3)
H C	66	Left hemiparesis	180	190/110		Urea nitrogen, 11.2, sugar, 124	Trace of albumin, granular casts	(3)
M W	51	Left hemiplegia, chronic endocarditis, cerebral embolism, arteriosclerosis	200+	220/115 310+150	3,000,000, hemoglobin, 65%	Urea nitrogen, 10.3, sugar, 97	Trace of albumin	Right eye, plus, left eye, glaucomatous cupping, (5), arterio sclerosis (1)
J O	48	Diabetes, arteriosclerosis	Normal	120/80	4,818,000	Urea nitrogen, 12.6, sugar, 155, cholesterol, 176	Negative	(2), arteriosclerosis, case of nephrosis (2)
B K	59	Left hemiplegia, cerebral thrombosis	150-160	150/80 120/80		Urea nitrogen, 12.5, sugar, 178 May 11, 1923, urea nitrogen, 11.7 Normal	Albumin, 4 plus, no casts	(2), arteriosclerosis, case of nephrosis (2)
M E I G	58 49	Postencephalitic condition Hypertension, right hemiplegia	150-160 170-180	152/100 170/100	Normal		Negative Negative	(2) (3)
P K	59	Arteriosclerosis, tumor of the spinal cord	160	165/105			Negative Albumin, 4 plus	(2) (1)
P L	60	Aortic insufficiency, auricular fibrillation	150	210/88		Urea nitrogen, 21, sugar, 97	Negative	Arteriosclerosis, (2), arteries narrow (3), muscular degeneration
S P	49	Postencephalitis, parkinsonian syndrome	170	130/80 160/80	4,000,000, hemoglobin, 85%	Urea nitrogen, 16.5, sugar, 107	Negative	
B B	49	Polycythemia, hypertension, general arteriosclerosis, angina pectoris, neurasthenia	170-180	218/210	7,800,000 hemoglobin, 130%		Negative	
A W	52	Hypertension	180	206/110 265/110		Urea nitrogen, 16.5, sugar, 133	Trace of albumin, granular casts	(3), sclerosis of cho roidal blood vessels, peripapillary atrophy Narrow, pale arteries
J S	61	General arteriosclerosis and hypertension, hemiplegia, emphysema and bronchitis, cardiac hypertrophy and dilatation	200+	200/110	5,760,000, hemoglobin, 100%		Negative	
A T	61	Chronic nephritis, hypertension, cardiac dilatation	200+	168/85 230/150	2,830,000, hemoglobin, 58%	Urea nitrogen, 58, creatinine, 4.36	Albumin, 3 plus	(5), plus
H D	57	Diabetes mellitus, peripheral neuritis	140	142/8	6,100,000, hemoglobin, 90%	Urea nitrogen, 12.3, sugar, 273, cholesterol, 133	Negative	(1), plus
S R	63	General arteriosclerosis and atherosclerosis, dilatation of aorta, cardiac hypertrophy and dilatation	160	154/80	5,200,000, hemoglobin, 85%		Negative	(2)

* In this table, ♂ indicates male, ♀, female

Observations in Cases of Arterial Disease—Continued

Name	Age, Years	Sex*	Diagnosis	Estimated Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg per 100 Cc	Urine	Retinal Changes
A S	60	♂	Diabetes, hypertension	150	172/100	hemoglobin, 88%	Urea nitrogen, 15.6, sugar, 276-307	Trace of sugar	Diabetic retinitis with hemorrhage and exudates (1)
O R	71	♂	Emphysema and chronic bronchitis	Normal	102/60			Negative, a few hyaline casts	(2)
R R	63	♂	Right hemiplegia, general arteriosclerosis	160	118/86 140/70 190/110		Urea nitrogen, 14.4, sugar, 178	Negative	(5)
S R	62	♂	Left hemiplegia	200	188/126 212/126		Urea nitrogen, 13.7, sugar, 115	Negative	(1)
H B	39	♂	Hemiplegia, emphysema	Normal	170/124 140/85	4,920,000, hemoglobin, 90%	Urea nitrogen, 11, sugar, 105	Negative	(2), plus, sclerosis of choroidal blood vessels (1), plus
S H	52	♂	Myocarditis, hypertrophy, dilatation, general arteriosclerosis, nephritis	160-170	142/88 172/120		Urea nitrogen, 28.7, sugar, 96	Albumin, 2 plus, granular casts	
J W	61	♂	Hemiplegia	150	90/58 156/100		Urea nitrogen, 15.4, sugar, 100	Negative	
H S	73	♂	Dilatation of aorta, atherosclerosis, extrasystoles, general arteriosclerosis	160	170/85 185/100		Urea nitrogen, 22.8, sugar, 122	Trace of albumin, hyaline casts	Retinitis like diabetic arteriosclerosis, (2)
L P	57	♂	Right hemiplegia	170	170/95 178/94	4,100,000, hemoglobin, 80%	Urea nitrogen, 15.9, uric acid, 2.4	Negative	(2), plus
O S	60	♂	Multiple cerebral hemorrhage	200	136/94 154/100		Urea nitrogen, 24.2, sugar, 121	Trace of albumin	(5)
J D	49	♂	Right hemiplegia, hypertension, aortitis	190	195/120 164/124	4,712,000, hemoglobin, 88%	Urea nitrogen, 11.9, sugar, 100	Trace of albumin	(4)
I P	60	♀	Cerebral tumor	190	185/100		Urea nitrogen, 11.9, sugar, 113	Trace of albumin	(4), degenerative changes in the macula, disks hyperemic
M S	45	♂	Tuberculous	170	120/80 156/96 186/122	3,450,000, hemoglobin, 78%	Urea nitrogen, 26.2, sugar, 108	Wassermann 2 plus	Simple primary optic atrophy, disseminated choroiditis, arteries (2), plus
B W	55	♂	Aortic and mitral insufficiency, coronary disease, hypertension	160/70	166/82 172/86	5,600,000, hemoglobin, 78%	Urea nitrogen, 8.4, sugar, 103	Albumin, 3 plus, hyaline and granular casts	(6)
R L	52	♀	Hypertension, cardiac hypertrophy and dilatation, chronic nephritis	200+	240/133 235/130	3,200,000, hemoglobin, 63%	Urea nitrogen, 89.6, sugar, 120	Albumin, 3 plus, hyaline casts	
G E	40	♀	Hypertension, general arteriosclerosis, endocrine disease	High?	155/105	4,000,000, hemoglobin, 95%	creatinine, 9.1 Urea nitrogen, 15.9, sugar, 97	Slight trace of albumin	Right eye, narrow and pale arteries, disk pale, left eye, narrow arteries, good color (4) and some perivascularitis
B B	59	♀	Hemiplegia, hypertension	200+	194/110			Slight trace of albumin	

B B	SS	♀	Hypertension, hypertrophic emphysema, hemiplegia	130	230/130		Urea nitrogen, 11, uric acid, 37, sugar, 103, cholesterol, 270	Negative	(1), arteries normal in color but seem contracted in places, essential hypertension (2)
A M	60	♂	Diabetes, advanced general arteriosclerosis	Normal	124/60 135/70	3,848,000, hemoglobin, 73%	Sugar, 3 plus		
R N	47	♀	Hemiplegia, hypertension, general arteriosclerosis, cardiac hypertrophy and dilatation	Elevated ?	106/130	1,700,000, hemoglobin, 85%	Albumin, plus, hyaline and granular casts, specific gravity, 1.028 Slight trace of albumin	Arteries pale and narrow, no other change	
P M	53	♂	Emphysema, general arterio sclerosis, relative mitral insufficiency	200	210/120		Urea nitrogen, 23, sugar, 106		(6)
I S	53	♂	Right hemiparesis, syphilis ?	200+	214/130		Urea nitrogen, 21 6, sugar, 103	Negative, Wassermann negative	(7)
I I	58	♀	Essential hypertension	Normal	210/100 170/80 160/85 170/80	3,600,000, hemoglobin, 67% 5,200,000, hemoglobin, 100%	Negative	Negative	(1)
S F	63	♀	Cancer of left breast, metastases	160-170					(2), plus
M C	58	♂	Hypertension, general arteriosclerosis	180-190	210/110 230/135 135/66 140/70 160/100		Urea nitrogen, 13 3, sugar, 101	Trace of albumin	(3), arteries very narrow
M B	66	♂	Left hemiplegia	Normal			Urea nitrogen, 13 2, sugar, 132	Negative	(1)
A K	68	♂	Right hemiplegia	170		1,800,000, hemoglobin, 85%	Urea nitrogen, 14 7, sugar, 116	No specific gravity obtainable	(3), opacity, vitreous degenerative changes of left eye, evidence of blocking of retinal artery
H M	54	♂	Right hemiplegia	160	130/48 170/70 180/95			Negative	(3)
N H	74	♀	Cardiac hypertension and dilatation, mitral insufficiency, hypertension, chronic nephritis, hemiplegia, aphasia	180				Negative	
B G	55	♀	Hypertension, chronic nephritis, cardiac hypertrophy, essential hypertension	160	174/86 200/98	3,190,000, hemoglobin, 78%	Urea nitrogen 17 5, sugar, 100	Negative	(2)
A F	56	♂	Postencephalitic, parkinsonian syndrome	Normal	120/90			Negative	(1)
M T	58	♂	General arteriosclerosis, cardiac hypertrophy and dilatation, hypertension intermittent claudication	160	134/88	4,330,000, hemoglobin, 83%		Negative	(2), changes in macula
D R	52	♀	Hypertension, cardiac decompensation, cerebral hemorrhage	200+	236/120	4,530,000, hemoglobin, 75%	Urea nitrogen, 27 4, uric acid, 47, sugar, 99	Negative	(5)
R W	53	♀	Cardiac hypertension and dilatation, left hemiplegia, arrhythmia, atheroma of aorta	200+	300/110		Urea nitrogen, 9 2, uric acid, 42, sugar, 121	Casts and good trace of albumin	(5)

* In this column, ♂ indicates male, ♀, female.

Observations in Cases of Arterial Disease—Continued

Name	Age, Years	Sex	Diagnosis	Measured Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg per 100 Cc	Urine Albumin at Intervals	Retinal Changes
S W	59	♀	Carcinoma of pleural cavity, mitral insufficiency, hypertension	160	165/95 to 212/110		Normal		
A O	65	♀	Right hemiplegia, cardiac hypertrophy of left breast, metastases	180-190	180/110			Negative	(3) - (4)
S O	70	♀	Carcinoma of left breast, metastases	160	160/90	4,310,000, hemoglobin, 70%	Urea nitrogen, 11.9, sugar, 123	Negative	(2)
S S	63	♀	Carcinoma of breast	160	100/65 124/80	3,650,000, hemoglobin, 65%	Urea nitrogen, 12, sugar, 96	Negative	(2)
H J	66	♂	Pseudobulbar palsy	Normal	102/63 202/102		Urea nitrogen, 11.1, sugar, 159	Negative	(1), evidently a case of essential hypertension
A K	60	♂	General arteriosclerosis, cardiac hypertrophy, angina	200-4	195/65 208/108		Urea nitrogen, 19.7, sugar, 116	Trace of albumin	Glaucoma of right eye, atrophy of disk, retinal arteries, (5)
A H	15	♂	Left hemiplegia, general arteriosclerosis	200	180/104			Trace of albumin	(5)
A G	♂	45	Mitral stenosis and insufficiency, auricular fibrillation	Normal	May 7, 1926, 120/70, June 3, 1926, 208/110		Urea nitrogen, 18.2, sugar, 117	Negative	Normal
M E	34	♂	Tubes	?	130/80	4,600,000, hemoglobin, 80%		Negative	Optic atrophy which looked like partly simple and partly postneuritic, narrow blood vessels (2)
D P	♂	37	Carcinoma of right breast, metastases to skeleton and cerebrum	160	150/90	3,200,000		Negative	(4)
J W	47	♂	Chronic nephritis, arteriosclerosis, dilatation of aorta	190	196/120		Urea nitrogen, 14.7, sugar, 119	Negative	(4)
A K	58	♂	Angina pectoris, hypertension	150	140/70 142/106		Urea nitrogen, 9.8, sugar, 124	Negative	(1)
R O	10	♂	Neoplasm of left kidney	Normal	85/85	1,600,000, hemoglobin, 30%	Urea nitrogen 9.1, sugar, 90	Negative	Optic atrophy, pale arteries, sclerosis of choroidal blood vessels (4)
E S	64	♂	Mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertension and dilatation, arrhythmia, chronic pulmonary emphysema	200	194/102	4,000,000, hemoglobin, 70%	Urea nitrogen, 18.7, sugar, 102	Albumin, moderate trace, a few granular casts	(5)
F F	56	♂	General arteriosclerosis, cardiac degeneration	200	154/100 190/108	3,940,000, hemoglobin, 70%	Urea nitrogen, 28.3, uric acid, 4.8 sugar, 103	Albumin, plus	(5)

I G	40	♂	Hypertension, right hemiplegia	180	170/100	Urea nitrogen, 18.9, sugar, 104	Negative	(3), some arteries partially obliterated (1), plus, ease of nephritis rather than arteriosclerosis
D P	66	♂	General peripheral arteriosclerosis, atheroma of aorta, diabetes, gangrene of left foot	Normal	110/70 144/63	Urea nitrogen, 13.3, sugar, 106	Albumin, plus, trace of sugar	(1), plus, ease of nephritis rather than arteriosclerosis
S S	54	♂	Chronic nephritis, general arteriosclerosis	200+	216/138 200/134 230/110 160/92	Urea nitrogen, 8.8, sugar, 103, cholesterol, 164 Urea nitrogen, 33.3, sugar, 107, cholesterol, 173 Urea nitrogen, 15.5, sugar, 125	Albumin, plus, granular casts Diastolic, 3 plus	(6) (3)
F S	63	♂	Angina pectoris, coronary disease, endarteritis obliterans	170	165/78 204/84 180/70 150/63	Specific gravity, 1.018, albumin, plus, trace of sugar, white blood cells and red blood cells, no casts		(1)
F A	60	♀	Hypertension, diabetes (?)	Normal	Before attack of hypertension blood pressure subnormal for age, about 130			
F M	65	♀	Diabetes mellitus, polyneuritis, hypertension, general arteriosclerosis	200	115/27 182/104	Urea nitrogen, 14.7, sugar, 120	Negative	(6)
F E	45	♀	Diabetes mellitus	High	L, 130/79 R, 160/100 Before entering hospital, 210/100	Specific gravity, 1.020, slight trace of dextrose, red blood cells numerous		(4)
S E	70	♀	Diabetes mellitus, general arteriosclerosis, cardiac dilatation and hypertrophy	Normal	138/53	Urea nitrogen, 12.5, sugar, 301	Albumin, 2 plus, otherwise negative	Diabetic retinitis, arteries normal in size, showed slight increase in reflex yet had exudates and hemorrhage, blood pressure should be normal
L S	62	♂	Left hemiplegia, general arteriosclerosis	200	240/130 230/130	Urea nitrogen, 39.3, sugar, 138, creatinine, 2.5	Albumin, 3 plus	(5)
A F	49	♂	Hypertension, emphysema, cardiac hypertension and dilatation, cardiac arrhythmia, angina	190	147/116 160/116	Urea nitrogen, 20, sugar, 112		(3), plus
H S	66	♀	Hypertension, chronic pulmonary edema, bronchitis, relative mitral insufficiency, general arteriosclerosis	190	178/106 210/100	hemoglobin, 68%, picture of pernicious anemia hemoglobin, 80%	Albumin, plus	(3) - (4)
L S	58	♀	Hypertension, moderate general arteriosclerosis, extra systoles, angina, cardiac hypertrophy	200+	205/115	Urea nitrogen, 13.2, sugar, 160	Albumin, 3 plus, sugar, plus, hyaline casts, plus, granular casts	Very narrow arteries and uneven in caliber
J B	66	♂	Hypertension, general arteriosclerosis, diabetes, cardiac arrhythmia	200+	215/118	Urea nitrogen, 12.9, sugar, 170	Albumin, 4 plus, sugar, 2 plus	(5) (?), arterial walls in good condition but contracted in places
L S	55	♂	Cerebral neoplasm	Over 200	230/80	Urea nitrogen, 17.4, sugar, 101	Negative	(7)

* In this column, ♂ indicates male, ♀, female

atrophy of the retina and pigment epithelium The choroid is clearly seen, and the choroidal blood vessels are light red or almost white and sharply outlined, giving the picture of a marked "tesselated" fundus (Islands of choroidal pigment are clearly seen)

There is another type of arteriosclerosis which might be called endarteritis obliterans, which is characterized by extremely narrow arteries, sometimes affected with perivasculitis, and accompanied by optic and retinal atrophy without the usual picture of tortuosities, exudates and hemorrhages This type is associated with a blood pressure of over 200 Blocking of the central retinal artery or its branches may occur, usually, in the event of a temporary lowering of the blood pressure

Such narrow arteries may sometimes be seen in retinitis pigmentosa, in which the blood pressure is not elevated

High blood pressures are sometimes seen in patients who show hardly any sclerotic changes in the retinal arteries In these cases the blood pressure is due to contraction of the arteries, and is marked by frequent variations in the degree of elevation The urine is usually normal The results of the chemical examination of the blood are apparently normal Contracted arteries with irregular caliber, though of good color, may sometimes be seen in the fundus This is generally known as essential hypertension Patients may have transient cerebral attacks or intermittent claudication in the presence of high blood pressure, sometimes the blood pressure is normal Contraction of the arteries may possibly be brought about by some change in the blood chemistry (such as increased cholesterol) or internal secretions or by the presence of bacterial toxins in the blood The mechanism may be analogous to intermittent asthma I have found a number of patients of this type in whose cases the diagnosis of hypertension with general arteriosclerosis was made The appearance of the fundus put a different aspect on these cases It has been proved that contraction of the arteries can occur I can cite instances of such occurrence, which I observed during the entire process

H. N., a young man, aged 23, came to my office complaining of attacks of blindness in the lower field of his right eye, which during three weeks previous to his visit recurred at intervals of three or four days This blindness would last one or two minutes His fundi were normal, and his retinal arteries were normal, his blood pressure was normal, he had an old mitral lesion While I was explaining to him that these attacks were caused by a transitory disturbance of the circulation, the patient suddenly called my attention to the fact that he was just having one of these attacks Taking him into the dark room without delay, I noticed that the upper branch of his retinal artery disappeared from view While observing the fundus with the ophthalmoscope, I noticed a sudden rush of blood into the invisible artery Simultaneously with the reappearance of the artery, the patient exclaimed that he could see again

Recently, I saw a case in which there were similar attacks, that of a young woman, M. B., aged 23, who also had an old mitral lesion. For some reason, contraction was limited in this case to a branch of one retinal artery. A similar contraction of the coronary artery would cause angina. One does see cases of angina pectoris, without elevation of blood pressure, in which relief is obtained by nitroglycerin. It would be easy to understand that such contraction partially sustained in many places of the body, particularly in the kidney and other organs, would produce a functional hypertension.

Such contraction, if prolonged, could produce symptoms and damage caused by blocking of an artery. This would explain cerebral cases in which arteriosclerosis is not present. In actual arteriosclerosis, connective tissue replaces the unstriated muscle of the arterial wall, contraction gradually becomes less possible, and persistent high blood pressure is then brought about by the narrowing of the lumen of the arteries caused by sclerosis and hypertrophy of the heart.

Finally, I want to state definitely that in postmortem examination of the retinal arteries, the microscope does not disclose moderate changes, although such were recognized with the ophthalmoscope.

CONCLUSIONS

In going over the cases which I have compiled, the following conclusions may be drawn:

- 1 The height of the blood pressure is generally in proportion to the changes in the retinal arteries.
- 2 High nitrogen content of the blood is also usually in proportion to the changes in the retinal arteries. A high blood pressure seems to keep the urea nitrogen and kidney function normal in some cases.
- 3 In cases of advanced retinal arteriosclerosis, the urine is never normal, in incipient and moderate cases, it is frequently normal.
- 4 In the presence of normal retinal arteries a high blood pressure generally has a functional cause and is usually associated with a normal blood chemistry and kidney function.
- 5 In cases of auricular fibrillation, the blood pressure is frequently higher than one would expect from the appearance of the retinal arteries.
- 6 Patients with incipient and moderate arteriosclerosis without much elevation of blood pressure may suffer from hemiplegia or coronary disease with angina, probably caused by either contraction (spasm) of the arteries or thrombosis of a branch of an artery or vein.
- 7 Retinitis in the presence of good arteries is caused by toxemia or changes in the blood chemistry, such as is found in diabetes. It is not necessarily accompanied by elevation in blood pressure. It has no bear-

ing on prognosis, if the general condition is under control. Thromboses of veins give the fundus the spurious appearance of advanced arteriosclerosis, and careful inspection of the vessels of both eyes will give the examiner a clearer conception of the actual condition of the arteries.

8 Incipient changes in the retinal arteries are frequently unrecognized, even by many ophthalmologists, and reports on the condition of the fundus are often either misleading or insufficiently helpful.

9 Contractions of the arteries in normal and in incipient cases may be toxic in origin. In these cases, clinicians could concentrate on the removal of the cause and lowering of the blood pressure, without risk to the patient.

I wish to stress the importance of a close association of the internist and ophthalmologist, whose careful ophthalmoscopic report as an aid in diagnosis and prognosis should be taken more seriously than in the past.

SCLERODERMA AND CALCINOSIS¹

ROBERT H. DURHAM, M.D.

DETROIT

CONTENTS

Incidence of Scleroderma

Pathologic Process and Pathogenesis of Scleroderma

Incidence of Calcinosis

(a) Of Skin and Subcutaneous Tissues

(b) About Joints

Theories as to Pathogenesis of Calcinosis

Review of Cases in the Literature

Author's Case

Laboratory Observations

Comment

Summary

The subject of scleroderma has long been and continues to be one of pertinent interest, as evidenced by the vast amount of literature published on the subject during the past half century and even before. Similarly, the conditions resulting from disturbed or pathologic calcium metabolism have commanded increasing attention during recent years. The infrequent combination of these two interesting conditions, scleroderma and pathologic calcification, or calcinosis,¹ is the unusual clinical problem I wish to present.

The condition now termed scleroderma was not unknown to ancient medical men. Hippocrates, according to Bertolotti,² described in his "Traité des épidémies," the case of a certain Athenian whose skin was so indurated that it could not be pinched. Galen, in his "Traité de thérapeutique," made note of a malady which he called "stegnose," described as a sort of obstruction of the pores of the skin with thickening, white spots, pigmentation and the absence of sweat glands. According to Arning,³ in 1752, Curzio described a case of a peculiar

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1 Although the word calcinosis not infrequently appears in the medical literature, it is not found in medical dictionaries or in the new English dictionary. Its exact meaning is, therefore, undefined. Presumably it refers to local, multiple or generalized pathologic calcium deposits regardless of location. Its most frequent use has been with reference to such deposits in the skin and subcutaneous tissues.

2 Bertolotti, M. M. *Etude radiologique d'un cas de sclerodermie avec le syndrome de Profichet*, *Nouv. iconog. de la Salpêtrière* **26**: 291, 1913.

3 Arning, quoted by Kaposi, in *Hebra: Diseases of the Skin*, New Sydenham Society **3**: 104, 1874.

induration of the skin under the title, "Dissertation anatomique et pratique sur une maladie de la peau d'une espece fort rare et fort singuliere." But the honor of describing, in 1845 (*Gazette Médecine de Paris*), the first authentic case of scleroderma and introducing the title "Du sclereme chez les adultes" goes to Thirial. In 1854 Gillette⁴ recapitulated twelve cases. Numerous other articles followed, and in 1894, Lewen and Heller⁵ collected 507 cases. Innumerable articles have appeared since.

The first authentic report of calcinosis in association with scleroderma was described by a Swiss physician, Weber,⁶ in 1878. Weber, however, interpreted the condition in his case as a form of gout. Although Lewen and Heller did not specifically differentiate cases in which calcareous depositions were present, a careful review of their monograph reveals descriptions which suggest that in six of their collected reports there was an associated calcification of the skin or subcutaneous tissues. A group of cases was not reported until 1911, when Thibierge and Weissenbach⁷ described a patient who had combined scleroderma and sclerodactylia with calcinosis, and collected eight other cases from the literature. The literature has not been recapitulated since the date of their publication.

INCIDENCE OF SCLERODERMA

Scleroderma is not a rarity, and a few cases are seen each year in any large clinic. The 507 cases collected by Lewen and Heller apparently covered the interim from the publication of Thirial's article in 1845 to the date of their publication in 1895. I am reviewing the 645 reported cases of scleroderma in the medical literature from 1894 to 1926. The disease seems most prevalent in middle life, occurring most often between the ages of 20 and 40. Fifty-one cases of scleroderma neonatorum were found in this group. Many cases, however, occurred in elderly adults. Geographically, the disease is widely distributed. Of the 645 cases, 25 per cent occurred in France, 20 per cent in Germany, 16 per cent in England, 14 per cent in the United States, 7.5 per cent in Italy and 4.5 per cent in Russia. From the data at hand, it seems doubtful if the review of this large series of cases will contribute many new facts about the subject. The study is, however, affording an insight into the large variety of types, the unusual and sometimes bizarre

4 Gillette, quoted by Kaposi (footnote 3)

5 Lewen, G., and Heller, J. *Die Sclerodermie*, Berlin, 1895

6 Weber, H. *Cor-Bis schweiz Aertze*, 1878, p. 622

7 Thibierge, G., and Weissenbach, A. J. *Concretions calcaires souscutanées et sclérodermie*, *Ann. de dermat. et syph.* 2: 129, 1911

associated conditions, and the divergent ideas as to etiology. The therapeutic agents described are many. It is interesting to record that spontaneous remissions were noted several times.

PATHOLOGIC PROCESS AND PATHOGENESIS OF SCLERODERMA

The pathologic process obviously is dependent on the type of the disease and its stage. Hypertrophy of the collagenous intercellular tissue is common to all types. The essential histologic changes consist of hypertrophy of the preexisting connective tissue bundles, followed by pressure on the vessels and epidermic structures. There is a considerable degree of perivascular and periglandular infiltration (lymphoid cells) and the papillae are at first swollen but later shrunken and flattened. The elastic tissue may be slightly increased in amount.

Innumerable theories have been advanced as to etiologic factors. After an analysis of 507 cases, including 28 autopsies, Lewen and Heller concluded that the pathologic process was dependent on an angioneurotic disturbance involving the peripheral as well as the central nervous system. A disturbance of various organs of internal secretion, particularly hypofunction of the thyroid gland, is a favorite theory. Recently, however, Marinesco and Goldstein,⁸ in addition to collecting a number of cases with atrophy of the thyroid gland, found 26 cases associated with exophthalmic goiter. Others think that the cause is an increased tonus due to vasoconstrictor substances acting on the sympathetic nervous system. Touchard⁹ believes it is an intermittent secretion of epinephrine. Kaposi,¹⁰ Kobner,¹¹ Lassar,¹² Unna,¹³ Nothhaft¹⁴ and others feel that a change in the lymphatic glands due to protracted constriction produces hypertrophy of the collagenous tissues. Changes of the spinal cord have been described in autopsy reports in several instances. Vidal,¹⁵ Crocker,¹⁶ Bales,¹⁷ and Newman¹⁸ think that it is

8 Marinesco, G, and Goldstein, M. Syndrome de Basedow et sclérodémie, *Nouv. iconog. de la Salpêtrière* **26** 272, 1913.

9 Touchard, quoted by Ravogli, A. A Rare Form of Scleroderma, *J. Cutan. & Genito-Urin. Dis.* **35** 1, 1917.

10 Kaposi in Hebra. Diseases of the Skin, New Sydenham Society **3** 104, 1874.

11 Kobner, quoted by Ravogli (footnote 9).

12 Lassar, quoted by Ravogli (footnote 9).

13 Unna. Die Histopathologie der Hautkrankheiten, Berlin, 1894.

14 Nothhaft, quoted by Ravogli (footnote 9).

15 Vidal, quoted by Ravogli (footnote 9).

16 Crocker. Diseases of the Skin, Philadelphia, 1908, p. 618.

17 Bales, quoted by Ravogli (footnote 9).

18 Newman, quoted by Luthlen in a Mracek. Handbuch der Hautkrenkheiten, 1904, vol. 3.

a condition of the blood vessels Dinkler¹⁹ and Gaucher²⁰ also feel that it is a condition of the small arteries of the skin Brown and O'Leary²¹ studied the capillaries in five cases of scleroderma with a view of determining whether or not the finer vascular changes noted might be an etiologic cause They concluded that the capillary deficiency and alteration peculiar to this disease did not precede the pathologic hypertrophy of the connective tissue bundles Certainly there is not as yet enough uniformity of opinion to permit the acceptance of any single pathogenic factor as a cause of scleroderma

INCIDENCE OF CALCINOSIS

Pathologic deposits of calcium in tissues have been reported in almost every portion of the anatomy, in muscle tendon, pericardium, myocardium, pleura, prepuce, scalp, eye and umbilicus, in all glands of internal secretion and in all the excretory organs The incidence of local deposits in the skin is not frequent It has been noted in a variety of conditions as follows as calcium metastases in the skin, following local injury, in caseous tuberculous nodules, in carcinomas of the skin or in metastatic ossifying sarcoma (Finnerud²²), on the basis of chronic inflammatory processes (Sehrt²³ includes syphilis and chronic dermatoses in this group) and as calcification of minute fat lobules These are the solitary or multiple, freely movable lesions found in the skin of the extensor surface of the legs of old persons

Kuznitsky and Melchior²⁴ found calcareous deposits in the skin in a case of universal fat atrophy, atypical lipodystrophia progressiva

In many cases, both the skin and subcutaneous tissues are involved It is evident that a sharp grouping cannot be made, as subcutaneous deposits of calcium also occur in the following conditions various forms of tumors, including lipomas, fibiomas, sebaceous cysts, sebaceous adenomas, "benign epitheliomas" and cystic adenomas connected with the sweat apparatus, subcutaneous veins and arteries (subcutaneous phleboliths), subcutaneous inflammatory nodules or scars, subcutaneous

19 Dinkler, Max Zur Lehre von der Sclerodermie, Heidelberg, 1891

20 Gaucher, Philippe Charles E Maladies de la peau, Paris, 1909

21 Brown, G E, and O'Leary, P A Skin Capillaries in Scleroderma, Arch Int Med **36** 73 (July) 1925

22 Finnerud, C W Ossifying Sarcoma of the Skin Metastatic from Ossifying Sarcoma of the Humerus, Arch Dermat & Syph **10** 56 (July) 1924

23 Sehrt, E Ueber Knochenbildung in der Haut, Virchows Arch f path Anat **200** 395, 1910

24 Kuznitsky, E, and Melchior, E Subcutane Lymphsackbildung und Kalkablagerungen in der Haut bei universellena Fettschwind, Arch f Dermat u Syph **123** 133, 1916

cysticerci, subcutaneous calcification in traumatic fat necrosis as in tissue in the breast, well described by Lecene and Moulonquet,²⁵ also by Lee and Adair²⁶

Riehl²⁷ noted deposits of calcium in the subcutaneous tissues in a case of leukemia

Calcinosis of Skin and Subcutaneous Tissues—Several such cases appear in the French and Italian literature under the title of "Profichet's syndrome"²⁸ Rather extensive calcinosis of the skin and subcutaneous tissues may appear without any apparent primary disease Lhermitte²⁹ records a case of generalized subcutaneous calcification of unknown etiology Morse³⁰ describes a case of extensive calcification of the skin and subcutaneous tissues in a child, aged 3½ years, occurring in areas of fat necrosis The lesions had been present one year The calcification was present at the borders of both axillae, at the left elbow, over the upper inner part of the thigh and buttocks, in the popliteal spaces and in the calves of both legs There was no evidence of infection Microscopic examination showed areas of degeneration of fat cells without cellular reaction Moise's interpretation of the process was "a primary degeneration of fat followed by calcification and repair by avascular organization without giant cell formation Lime seemed to deposit in the homogeneous hyaline material"³¹

This case of Morse's and the cases of calcification following traumatic fat necrosis described by Lecene and Moulonquet, and by Lee and Adair, seem to favor the hypothesis advanced by Klotz,³² in discussing the origin of calcification from calcium soaps He believes that the calcium is first laid down as soaps, later changing into the less soluble carbonate and phosphate

25 Lecene, P, and Moulonquet, P La cystosteatonecrose ou saponification intracellulaire du tissu cellulo-adipeux sous-cutané, *Ann d'anat path* 2 193, 1925

26 Lee, B J, and Adair, F E Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, *Ann Surg* 80 670, 1924

27 Riehl Proc 17th Intern Cong Med, 1913, section 13, pp 179 and 188

28 Profichet, G C Sur une variété de concrétions phosphatiques sous-cutanées (pierres de la peau), Thesis, Paris, 1900

29 Lhermitte, J La calcinose généralisée et ses formes anatomiques interstitielle et sous-cutanée, *Semaine méd* 30 553, 1910

30 Morse, J L Calcification of the Skin in a Child, *Am J Dis Child* 22 412 (Oct) 1921

31 It is of interest to note that Bernheim-Karrer (ueber Subkutane Fettgenekrosen beim Neugeborenen [Sog Sklerodermie der neugeborenen], *Schweiz med Wchnschr* 52 12, 1922) describes a case of subcutaneous fat necrosis without calcification occurring in association with scleroderma neonatorum

32 Klotz, O Studies upon Calcareous Degeneration I The Process of Pathological Calcification, *J Exper Med* 7 633, 1905

Weidman and Schaffer³³ have recently described a case of calcification of the skin, including the epiderm, with extensive bone resorption. The patient was an elderly man. The sections of the skin that were studied were taken from the hand, this is apparently the first case described showing calcification of the epithelial structures and peripheral nerves. Since the serum calcium was normal, these authors feel that their case also supports the theory of Klotz, that "in the process of calcification there is a preliminary fatty metamorphosis of tissue and the final calcification comes about through a series of intermediate changes in which soaps figure."

"Calcinosis universalis" is a title applied by Verse³⁴ in referring to several cases of generalized deposits. He calls attention to the early changes in the intercellular substance of the connective tissue. Tilp³⁵ and von Gaza³⁶ have each reported a case of diffuse or universal calcinosis of unknown etiology.

Karvonen,³⁷ Reines,³⁸ and Liesegang³⁹ each describes cases of cutaneous calcification. Other cases of subcutaneous calcification are reported each by Ruggles,⁴⁰ Mauclaure⁴¹ and Lesseliers⁴².

True bone formation may occur in the skin, in subcutaneous tissue or in scars. A case of calcinosis of the skin, which had progressed to osteoid tissue, has been described by Becker,⁴³ under the title, "Osteosis Cutis." He believes that the calcium deposition is but a preliminary step in the bone formation. Quoting Sehrt, Becker says "we are dealing

33 Weidman, F. D., and Shaffer, L. W. Calcification of Skin Including Epiderm in Connection with Extensive Bone Resorption, *Arch. Dermat. & Syph.* **14** 503 (Nov.) 1926.

34 Verse, M. Ueber calcinosis universalis, *Beitr. z. path. Anat. u. z. allg. Pathol.* **53** 212, 1912.

35 Tilp, A. Demonstration eines Falles von ausgebreiteter Kalzinosis, *Verhandl. d. deutsch. path. Gesellsch.*, 1910, pp. 277-279.

36 Von Gaza. Ueber Calcinosis interstitialis universalis, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **19** 372, 1912.

37 Karvonen, J. J. Thokivista (Cutaneous Calculi), *Duodecim*, *Helsing.* **19** 319, 1903.

38 Reines, S. Petrificatio cutis circumscripta, *Arch. f. Dermat. u. Syph.* **88** 267, 1907.

39 Liesegang, R. E. Ueber Kalkablagerungen der Haut, *Arch. f. Dermat. u. Syph.* **139** 73, 1922.

40 Ruggles, H. E. Calcified Deposits in the Soft Tissues of the Left Forearm, *Am. Atlas Stereo-roentgenol.* **1** 82, 1916.

41 Mauclaure. Calcul sous-cutane de la face posterieure de l'avant-bras, *Bull. et mem. Soc. anat. de Paris* **94** 488, 1924.

42 Lesseliers, E. A propos d'un cas de concrections calcaires sous-cutanes, *Bull. Soc. de med. de Gand* **75** 7, 1908.

43 Becker, S. W. Osteosis Cutis, *Arch. Dermat. & Syph.* **10** 163 (Aug.) 1924.

with primary tissue death with secondary calcification and subsequent metaplastic bone production by the connective tissue" Breda⁴⁴ also reports a case with calcareous concretions which proceeded to bony tissue. Cases of true bone formation probably occur, however, without evidence of previous calcification. Various theories have been tendered to explain this type. One is the metaplasia of connective tissue into osteoid tissue, with the formation of true bony trabeculae if lime salts are deposited. In brief, as summarized by Wells,⁴⁵ pathologic calcification occurs in tissues that have suffered partial or total loss of vitality, or that have undergone hyaline degeneration, whereas in ossification, the accumulation of lime salts is within the stroma or cells of tissue which have changed to a homogeneous ground substance, with vitality decreased but not lost. In the latter, there is diffuse, even permeation of the salts in the tissue, in calcification, the deposits of lime salts remain in clumps or fuse into masses. Any type of cell or tissue sufficiently degenerated may become calcified, and any area of calcification may then be replaced by bone. Ossification occurs only in varieties of connective tissue. Deposits of calcium salt anywhere can stimulate connective tissue to form bone, although in the absence of calcium salts, cells normally osteogenic will not form bone. Moschcowitz⁴⁶ emphasizes that ossification without preliminary calcification is not found. The vascular supply must also be a factor in the process of ossification, a probable reason why calcareous concretions within hollow organs such as the appendix never reveal bone formation.

Calcinosis About Joints—These cases are mentioned because they frequently occur in association with cutaneous or subcutaneous calcification, but a number of cases are reported in which the localization was around joints alone. The author has recently had five patients with deposits of calcium just outside the subdeltoid bursa. This condition is seen infrequently and probably differs in many respects from the cases with deposits in the soft parts near the joints of the phalanges or wrists. The latter type varies from fine deposits, called by French writers⁴⁷ "bony sand," to extreme calcification in soft tissues manifested as large visible tumors. Such a case of marked localized deposits has been observed by Hamlin,⁴⁸ who will publish it in detail. His patient, a

44 Breda, A. Concrezioni calcari e produzioni steiiformi nel connettivo sottocutaneo dell'uomo, *Gior ital d mal ven* **50** 244, 1915.

45 Wells, H. G. *Chemical Pathology*, ed 4, Philadelphia, W. B. Saunders Company, 1920.

46 Moschcowitz, E. Various Forms of Calcification and Ossification, *Proc New York Path Soc* **13** 19, 1913.

47 Quoted by Delherm, Morel-Kahn, and Couput. *Bull et mem Soc d radiol méd de Paris* **13** 110, 1925.

48 Hamlin, L. E. Personal communication.

young man, aged 23, had symptoms which began two years before observation and followed a local infection in the hand, caused by removal of a sliver with a jack-knife. Subsequently, small calcified nodules appeared around the phalangeal joints and throughout the soft tissues of the right metacarpus. These tumors have continued to increase in size and number. Two of the phalangeal joints became fluctuant, and many small calcareous nodules were discharged through a chronic sinus. X-ray examination showed heavy deposits of calcium salts, occurring as a fusion of innumerable small dotted areas scattered throughout the soft parts of the entire hand. There was particular localization around the phalangeal and metacarpal joints. The tendons or the tendon sheaths of the lower forearm also showed moderate calcification. X-ray examination of the remainder of the body did not show any other deposits or rarefaction of the bones.

Wildbolz⁴⁹ observed a case in which numerous nodules appeared around the joints of the hands and feet and later at the olecranon. The patient was a woman, aged 57, and the nodules had been enlarging and becoming more painful for six or seven years. Chemical examination of the concretion showed calcium carbonate, calcium phosphate and traces of magnesium. Uric acid and oxalic acid were absent. Microscopic examination showed the presence of leukocytes and giant cells, indicating an inflammatory process.

Ducasse⁵⁰ describes a similar case in a woman, aged 50. The concretions varied from 2 mm to 3.5 cm in diameter and were numerous over the extensor surfaces of the knees, elbows and fingers. Calcified concretions were also present in the main stem branches of the bronchi on the right side. The patient had previously expectorated concretions. Chemical analyses of the extruded deposits showed the presence of cholesterol and lime. Ducasse calls attention to the high cholesterol content in the blood in this case, 270 mg per hundred cubic centimeters.

Wilens and Derby⁵¹ report a case of multiple subcutaneous nodules of calcium in a boy, aged 5 years, occurring about the knee joints, in Scarpa's triangle, on the buttocks, the extremities and around the shoulder joints. The bulk of the deposits of calcium was in the fat and fibrous tissue of the subcutaneous layer. Fat necrosis did not occur as in Morse's patient.

49 Wildbolz, H. Ueber Bildung von phosphorsauren und kohlensauren Konkrementen in Haut und Unterhautgewebe, *Arch f Dermat u Syph* **70** 435, 1904.

50 Ducasse, R. R. Calcification of the Skin with Unusual Findings, *Arch Dermat & Syph* **7** 373 (March) 1923.

51 Wilens, G., and Derby, J. Calcification of Subcutaneous Tissue in Child (Calcinosis Universalis), *Am J Dis Child* **31** 34 (Jan) 1926.

Tisdall and Erb⁵² found extensive calcareous deposits over the epiphyses at both ends of the humeri, the proximal ends of the radii, ulnae and tibiae, and the distal ends of the femora, occurring in an infant 5 weeks of age

Another condition of disturbed calcium metabolism, now a recognized entity and differing entirely from the foregoing types, is the so-called metastatic calcification of Virchow, studied and described by Wells,⁵³ Schulze⁵⁴ and others. In these cases there is an over-saturation of the blood with calcium salts, and deposits may occur without tissue degeneration. Wells points out that the deposits occur where the carbon dioxide is least abundant. To date, he has been able to collect only thirty-two cases from all the literature. The case described by Weidman and Shaffer⁵⁵ showed bone resorption, although the serum calcium was normal. Cases of demobilization of calcium from skeletal bones without deposition in the superficial tissues are reported as occurring in sepsis. In the new light of studies of the parathyroid hormone, it is likely that this type of case is a result of disturbed parathyroid function. Certain cases in which the condition was regarded as metastatic calcification have been definitely associated with pathologic processes of the parathyroid glands. Thomas⁵⁶ reports a case of metastatic calcification in a boy in whom the two parathyroid glands were hypertrophied and measured 2 cm in diameter. There was marked calcification in the small arteries, a large calcareous plaque in the skin of the right buttock and rarefaction of the long bones. Hubbard and Wentworth⁵⁶ report hypertrophy of the parathyroid glands in a case of metastatic calcification associated with chronic nephritis. Harbitz⁵⁷ feels that nephritis may at times lead to enough calcium retention to account for metastatic calcification. Normally, however, the serum calcium content of the blood is reduced in nephritis.

THEORIES AS TO PATHOGENESIS OF CALCINOSIS

It seems generally agreed that inflammatory changes are not a constant factor in calcinosis, yet many cases seem definitely to have followed

52 Tisdall, F. F., and Erb, T. H. Report of Two Cases with Unusual Calcareous Deposits, *Am J Dis Child* **27** 28 (Jan.) 1924

53 Wells, H. G. Metastatic Calcification, *Arch Int Med* **14** 574, 1915, *Tr Chicago Path Soc* **9** 208, 1914-1915

54 Schulze, F. Skelettveränderungen als Ursache von Verkalkungen, *Mitt a d Grenzgeb d Med u Chir* **36** 243, 1923

55 Thomas, W. S., in discussion on Weidman and Shaffer. *Arch Dermat & Syph* **14**:503 (Nov.) 1926

56 Hubbard, R. S., and Wentworth, J. A. A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroid, *Proc Soc Exper Biol & Med* **18** 307, 1920-1921

57 Harbitz, quoted by Wells, H. G. (footnote 45, p. 443)

local inflammatory conditions In the earlier stages, round and giant cells are seen infrequently, later, the concretions may act as a foreign body and produce some irritation

Many observers have held that the deposits occur in or around degenerated tissue cells Jadassohn⁵⁸ did not find any degeneration of the elastic or connective tissue fibers at the site of recent deposits He feels, however, that the elastic fibers must be degenerated, though molecular and unrecognizable Pospelow⁵⁹ mentions the affinity between elastic fibers and calcium salts and feels that deposits can probably occur in normal elastic tissue⁶⁰

Wildbolz,⁴⁹ Licharoff⁶¹ and Lewandowsky⁶² all concur that the calcification is a disturbance of inorganic metabolism, similar in character to gout, except that calcium salts are deposited instead of urates

As to the mechanism of the calcium deposition, Pospelow feels that it is because the blood is saturated due to excessive amounts present, or because the solubility of calcium in plasma is changed, even though the amount of calcium in the blood has not risen above normal

Hofmeister⁶³ found that as soon as a fluid in any way loses its free carbonic acid (as when the latter is bound to an alkaline medium), a deposition of calcium phosphate can occur under the condition and that the velocity of the fluid flow or a higher protein content does not hinder this deposition Hofmeister also feels that the colloidal proteins play a rôle

Tashiro⁶⁴ holds the view that the occurrence of insoluble calcium salts at one point must be intimately associated with a metabolism which forms bases He states that calcification need not be preceded or accompanied by an abnormal amount of calcium in the blood, the essential thing is a local production of ammonia or other base forming compounds with a normal supply of calcium Infection, mechanical irritation or changes in physiologic metabolism may be other factors

58 Jadassohn, J Ueber Kaltmetastasen in der Haut, Arch f Dermat u Syph **100** 317, 1910

59 Pospelow, W A Ein Fall von Kalkablagerung in der Haut, Arch f Dermat u Syph **140** 75, 1922

60 Experimentally, Katase (Experimentelle Verkalkung am Gesunden Tiere, Beitr z path Anat u z allg Path **57** 516, 1913) injected calcium salts in animals and produced calcification in organs without previous injury to the cells

61 Licharoff, quoted by Pospelow Arch f Dermat u Syph **111** 75, 1922

62 Lewandowsky Ueber subkutane und periartikuläre Verkalkungen, Virchows Arch f path Anat **181** 179, 1905

63 Hofmeister Experimentelles über Gewebsverkalkung, München med Wchnschr **56** 1977, 1909

64 Tashiro, S Studies on Alkaligenesis in Tissues I Ammonia Production in the Nerve Fiber During Excitation, Am J Physiol **55** 519, 1922

Oliver⁶⁵ pictures tissue calcification as a process similar to the formation of gallstones, the production of ammonia and the destruction of bile salts. Lichtwitz⁶⁶ mentions the possible part colloidal proteins may play in the induction of calcification. He thinks that precipitation of colloids in degenerated tissues may bring about a reduction in soluble crystalloids whereby the more insoluble salts such as calcium are precipitated. Hunter⁶⁷ concludes that calcification is a terminal phase of the fibrosis, that an alteration of the vitality of the sclerosed tissue determines the deposit of lime salts, analogous to deposits of calcium elsewhere, as in sclerosed heart valves or in old tuberculous lesions.

Wells,⁴⁵ whose studies have been extensive, reviews the possibility that calcium is first bound as soaps. He was able to find only traces of calcium soaps in calcifying matter, and doubts if these soaps are an essential step in calcification, except in those cases in which areas of obvious fat necrosis are present. He feels that chemical precipitants in the tissue are not responsible, but that calcification depends on physicochemical factors and variations in the carbon dioxide concentration. He pictures calcification beginning as a simple physical adsorption by hyaline substance and dependent on the presence of a local alkalinity or perhaps a decreased amount of carbon dioxide in the fluids and tissues, and that calcification occurs whenever the proportion of calcium present in the blood is so great that it requires the effect of both the colloids and of the carbon dioxide in maximum concentration to keep it in solution.

In view of the number of divergent opinions reviewed, it is obvious that much confirmatory work remains to be done in order to establish universal agreement as to the applicability of one or more of these theories.

In summarizing, pathologic calcification occurs in almost all tissues of the body and at all ages. (Tisdall and Eib's⁵² patient was 5 weeks of age, and Goldreich⁶⁸ reported a case occurring in an infant, aged 7 weeks.) In those cases in which the deposits occurred in the skin and subcutaneous tissues, the usual chemical composition is calcium phosphate and carbonate and traces of magnesium. Rarely, cholesterol may be present. Uric acid is not present. Generally speaking, inflammatory changes are not a factor. The deposits are believed to occur in or

65 Oliver, quoted by Ducasse, R. R. Calcification of the Skin, *Arch. Dermat. & Syph.* **7** 373 (March) 1923.

66 Lichtwitz, L. Ueber die Bedeutung der Kolloide für die Konkrementbildung und die Verkalkung, *Deutsche med. Wchnschr.* **36** 704, 1910.

67 Hunter, W. K. Scleroderma with Subcutaneous Calcareous Deposits, *Glasgow M. J.* **79** 241, 1913.

68 Goldreich, A. Ein 7 Wochen Alter Knabe mit Zellgewebsverhartung, *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien* **13** 57, 1924.

around degenerated tissue cells. Numerous observers say that the deposits do not occur in normal tissues. In instances in which this appears to be the case, the theory is offered that toxins have lowered the vitality of the cells.

REVIEW OF CASES FROM THE LITERATURE

Scleroderma and calcinosis occur together most infrequently. It seems safe to say that less than a dozen cases had been reported prior to 1911. With a more prolific medical literature, a larger number of cases has since appeared.

In 1913, Bertolotti² observed and described in detail the clinical and roentgenographic study in a case of scleroderma accompanied by well marked acrocyanosis and sclerodactylia. The patient was a woman, aged 36, whose symptoms began at the age of 30. The scleroderma was maximum in the extremities. There were distinct bands about the elbows, knees and feet, in areas of which were scattered small indurated nodules of calcification. Similar concretions were also present in the soft tissues of the terminal phalanges and along the forearm in an area of scleroderma. Localized muscular atrophy resembling an interstitial myositis was also present. Most of the larger tendons were retracted, indurated and calcified. There was localized osseous atrophy in the terminal phalanges, symmetrical on the two sides. Comparative x-ray studies after a year's interval evidenced progressive resorption of the phalangeal bones. A chemical analysis of the concretions mixed within the horny layer showed the presence of calcium salts. There was a disturbance of internal secretions with atrophy of the thyroid gland and other signs of hypothyroidism, as well as roentgenographic evidence of hypophyseal hypertrophy. Although Bertolotti was unable to prove which process was primary, he believed that the condition resulting from the scleroderma favored the deposition of the calcium. He also cited other instances in which calcification had followed trophic and degenerative disturbances. The rather rapidly developing bony changes suggest that this is a case of metastatic calcification with scleroderma.

In 1913, Hunter⁶⁷ also reported a case of scleroderma with subcutaneous calcareous deposits associated with Raynaud's disease. The patient, a woman, aged 38, had suffered from symptoms referable to Raynaud's phenomena since 14 years of age. The scleroderma had been present since the age of 18, and subcutaneous concretions first appeared at the age of 21. The scleroderma involved the skin of both hands, lower arms, face, neck, back and buttocks. The calcified deposits were much more limited and were present around the joints of the fingers especially, and had been extruded from the skin around the metatarsophalangeal joints and from the region of the left elbow. Chemical

studies of the deposits showed the presence of carbonate and phosphate of calcium and magnesium. Uric acid was absent.

Previous reports of cases had been made in England or continental Europe. In 1917, Olson⁶⁹ described the case of a young woman, aged 27, who had sclerodactylia with sclerodermatous changes involving the palmar surfaces of the hands. Numerous small calcareous concretions were present in the tissues of the fingers and near the olecranon. They were composed largely of carbonates. Uricates and uric acid were absent.

A case of calcification about an ulcerated area of scleroderma of the face is described by Pollitzer.⁷⁰ The patient was a man, aged 47, of German descent. The scleroderma (diagnosed by Kaposi, Vienna) began on each side of the face nineteen years previous to examination, but later underwent a remission with marked improvement. Scattered areas of scleroderma reappeared on both sides of the face when the patient was 32 years of age, numerous ulcerations appeared with calcified plaques projecting through the ulcers and involving extensive areas of surrounding subcutaneous tissues. Chemical examination of the concretions was not recorded.

A case of scleroderma with small pleomorphic calcareous deposits occurring in a boy, aged 4, was reported by Langmead.⁷¹ The patient had an amentia of the mongolian variety, but not as marked as the average case. Bluish discoloration of the skin had been noted since birth. At the age of 3, scleroderma began to appear over the upper part of the arms, shoulders and thighs, with hard subcutaneous nodules varying "from minute areas to the size of a shilling." X-ray examinations showed a marked infiltration of calcareous deposits in the subcutaneous tissues involved. Symptoms of the joints involving the knees and ankles were developing. Although the fingers were small and shiny, definite sclerodactylia had not appeared.

In 1923, Bayless⁷² reported the case of a woman, aged 64, who had extensive scleroderma involving the hands, feet, chest and abdomen with large and small calcified nodules projecting through the skin of the hands, wrist and great toes. Nodules could not be palpated through the skin of the chest or abdomen. The scleroderma had been progressing for a number of years, arthritic symptoms had been present for seven years, small calcified nodules appeared on the back of the wrists four

69 Olson, G. M. Sclerodactylia with Calcareous Concretion, with Report of a Case, *J. Cutan. Dis. incl. Syph.* **35**: 96, 1917.

70 Pollitzer, S. Ossification in a Case of Scleroderma, *J. Cutan. Dis. incl. Syph.* **36**: 271, 1918.

71 Langmead, F. S. Scleroderma with Calcification in a Mongol, *Proc. Roy. Soc. Med.* **12**: 94, 1918-1919, *Sect. Dis. Child.*

72 Bayless, B. W. Scleroderma, *Kentucky M. J.* **22**: 39, 1924, *Radiology* **6**: 239, 1923.

years before X-ray examinations showed that these were unattached to the bone. An atrophic arthritis of the phalangeal articulations was present. There was marked contraction over the tips of the fingers suggesting an accompanying sclerodactylia.

Tisdall and Erb⁵² describe two unusual cases of calcification in children. One of their patients, a boy, aged 12, had extensive deposits of calcium in the subcutaneous tissues of both legs, arms and buttocks with generalized skin changes, the diagnosis of which rested between xeroderma pigmentosum and scleroderma. Biopsy and examination of a section of the skin containing a calcareous nodule resulted in a final diagnosis of scleroderma.

A case of scleroderma with sclerodactylia, accompanied by calcinosis or "calcium gout" was described by Merklen and Vallette⁷³ in 1924. The patient was a single woman, aged 55. Symptoms of scleroderma began to be manifested at the age of 42, coincident with her menopause. Two years later, well marked sclerodactylia had appeared, involving all the fingers. The scleroderma involved the hands, arms, face and neck. In the region of the left elbow and forearm, inflammatory areas appeared through which were extruded chalky concretions containing lime salts. Analyses did not show cholesterol or uric acid. Roentgenograms revealed the presence of numerous masses around the terminal phalanges and joints of fingers of both hands and around the elbow joint. In this case, the authors felt that the trophic disturbance of the skin preceded the appearance of the concretions. The calcification was found only in the areas of scleroderma.

Delherm, Morel-Kahn and Coupot⁷⁴ describe briefly the roentgenographic observations in two cases of scleroderma. In one, there was an ankylosis of the phalangophalangeal joints with disappearance of the articular space, the metacarpophalangeal joints remained unchanged. In the second case, there were also articular lesions, involving the metacarpophalangeal interspace with osseous rarefaction, more accentuated at the distal ends of the phalanges. Near the end of the phalanx of the index finger was a group of small deposits of calcium, numbering seven or eight, similar to "bony sand," but described "as the deposits seen in the cutaneous cellular tissues in the course of scleroderma."

A case in which there were subcutaneous calcium nodules on the fingers of both hands and at the elbow with sclerodactylia was reported by Davis⁷⁵ in 1912. The patient, a woman, aged 34, had suffered from

73 Merklen, W. M., and Vallette, A. Scleroderma avec concretions calcaires, *Bull. Soc. franç. de dermat. et syph.* **31** 120, 1924 (Reun. de Strasb.).

74 Delherm, Morel-Kahn and Coupot. Sclerodermie et lésions osseuses, *Bull. et mem. Soc. de radiol. med. de Paris* **13** 110, 1925.

75 Davis, H. Case of Raynaud's Disease Associated with Calcareous Degeneration, *Proc. Roy. Soc. Med.* **5** 99, 1911-1912, Dermat. Sect.

chilblains as long as she could remember and Raynaud's disease had been present for many years. The hard nodules first appeared eight years before while she was nursing her first baby. The nodules gradually worked their way through the skin and calcareous material was discharged for some time. Chemical examination showed the presence of calcium carbonate and phosphate.

In 1911, Scholefield and Weber⁷⁶ observed a similar case in an unmarried woman, aged 50. In childhood the patient began to have chilblains. At the age of 35, sclerodactylia was noted and progressed gradually. Subcutaneous concretions formed under the skin of the fingers and around the left olecranon. Extensive metabolic studies were not made. The concretions, however, did not contain urates.

Logan⁷⁷ reports a case of Raynaud's disease in a woman, aged 60, with numerous calcareous nodules on the lateral and flexor surfaces of all the digits. The patient had suffered from chilblains involving the hands, feet and ears as long as she could remember. Some of the lumps became acutely inflamed and ulcerated, extruding the deposits. Chemical studies showed the presence of phosphate and carbonate of lime, no trace of uric acid was present.

Symptoms and disorders of the joints frequently accompany scleroderma. In 1898, Dercum⁷⁸ noted and pointed out this frequent relationship. Claude, Rose and Bouchard⁷⁹ describe a case of scleroderma, sclerodactylia and chronic articular difficulty. Apert⁸⁰ has also reported a case of scleroderma with ankylosed joints in a child, aged 12 years. Other observers—Leontjewa,⁸¹ and Adrian and Roederer⁸²—also found arthropathies due to calcification accompanying scleroderma. More frequent x-ray studies would undoubtedly reveal a greater incidence of calcinosis about joints in cases of scleroderma.

Of interest, also, are two cases of scleroderma with subcutaneous fibrous nodules without calcification. The patient observed by Gray⁸³

76 Scholefield, R. E., and Weber, F. P. A Case of Sclerodactylia with Subcutaneous Calcification, *Brit J Dermat* **24** 200, 1912.

77 Logan, J. R. Unusual Calcareous Deposits in the Soft Tissues of the Hands, *Arch Radiol & Electroth* **28** 55, 1923-1924.

78 Dercum, F. X. On Scleroderma and Chronic Rheumatoid Arthritis, *J Nerv & Ment Dis* **25** 703, 1898.

79 Claude, Rose and Bouchard, quoted by Bertolotti (footnote 2).

80 Apert, E. Sclerodermie avec arthropathies ankylosantes et atrophie musculaire chez une enfant de douze ans, *Bull Soc franç de dermat et syph* **19** 244, 1908.

81 Leontjewa, L. A. Ueber veränderungen der Knochen und Gelenke bei Sklerodermie, *Arch f klin Chir* **128** 293, 1924.

82 Adrian, C., and Roederer, J. Les arthropathies au cours de la sclerodermie, *Ann de dermat et syph* **1** 299, 341 and 395, 1920.

83 Gray, A. M. H. Generalized Scleroderma with Subcutaneous Nodules, *Proc Roy Soc Med* **16** 107, 1922-1923, Sect Dermat.

had generalized scleroderma with innumerable subcutaneous nodules attached to tendon sheaths, capsules of joints and periosteum and on the backs of the hands and feet. Microscopic examination showed the presence of fibrous tissue that had undergone hyaline degeneration. It is interesting to speculate as to whether these hyaline changes were a forerunner of calcification. Bruhns⁸⁴ also describes a case of nodular tumors of the skin which were present over the abdomen, scapular region and left axilla. Typical scleroderma "en bande" was also present.

I shall add to the previous nine cases of scleroderma and calcinosis collected and reported by Thiberge and Wiessenbach, and to the foregoing thirteen cases reviewed (including three cases of sclerodactylia with calcinosis) the report of the case of another patient who came under my own observation.

AUTHOR'S CASE⁸⁵

A white woman, aged 67, about thirty-seven years before examination had an ulcer appear on the lower portion of the right leg, edema of both legs was marked at times, and small bone-like areas appeared in the cutaneous tissues, gradually becoming more numerous. The ulcers finally healed, but recurred at intervals. Active ulceration had been present on both legs for seven years. The skin over the lower part of the legs became tight and drawn. The small dots of bone-like deposits gradually became more numerous and fused into large plaques in and around the ulcerated areas. There was nothing to suggest the presence of syphilis or tuberculosis in either the personal or the family history. Varicose veins were not present. Small areas of calcification in patches of scleroderma were also present over the forehead. The skin of the fingers was tight and drawn. The lower third of both legs was pigmented, dark brown and scarred, and the skin was tight. Innumerable small calcified areas could be palpated just beneath the surface, and in many places they protruded through the skin, becoming fused into irregular plaques. X-ray examinations showed extensive subcutaneous calcified deposits in the lower half of both legs, and calcified nodules around numerous joints. The patient had advanced chronic nephritis and died from uremia. The serum calcium was 7.4 mg.

A postmortem examination showed extensive calcification through the entire vascular system. Several of the large arteries and veins had the form of a solid tube. A large calcified mass was present in the myocardium. The right saphenous vein was replaced by a solid chain of calcified nodules. Three parathyroid glands were present, and were of ordinary size. The histologic structure seemed essentially normal.

The gross anatomic diagnoses were generalized arteriosclerosis with extensive calcification, atheromatous ulcers, thrombus formation and aneurysmal dilatation of the aorta, phlebosclerosis, calcification of the mitral valve and adjacent myocardium, mitral insufficiency and slight stenosis, cardiac hypertrophy, sclero-

84 Bruhns, C. Ueber Knotenbildungen bei Sklerodermie, *Arch f Dermat u Syph* 129 178, 1921.

85 This case has been reported in detail (Durham, R. H. A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, *Ann Clin Med* 5 679 [Jan] 1927).

derma of the legs, hands and forehead, subcutaneous calcified nodules and plaques in the regions of the legs and elbow, ulcers of the legs, with pigmentation and old scars, limitation of motion of the knee joint, edema of the ankles, chronic nephritis (small granular kidney), acute purulent bronchitis, early lobular pneumonia, hyperplasia of the tracheobronchial and cervical lymph nodes, old scars of the apexes of the lungs, calcification of the bronchial lymph nodes, colloid adenomas and old scars of the thyroid gland, duodenal ulcer, cholelithiasis, localized hyaline thickenings of the splenic capsule and senility

TABLE 1—*Chemical Determinations of the Blood*

	Blood Serum Calcium	Calcium Whole Blood	Inorganic Phos- phorus	Phosphorus	Carbon Dioxide	Cholesterol	Fatty Acids	Sugar	Nonprotein Nitrogen	Uric Acid	Urea Nitrogen
Observations in Scleroderma and Calcinosis											
Tisdall and Erb ⁵²	97		44								
Merklen and Vallette ⁵³				77		107				23	42
Gitlow and Steiner Arch Derm & Syph 9:549, 1924	72 631				50	223		70	337	47	1125
Bayliss ⁵²				75				123		402	72 72
Durham ⁵⁵	76		477					89	37 60	396	173
Comparative Observations in Calcification without Scleroderma											
Calcium about joints in infant (Tisdall and Erb ⁵²)	93		45								
Calcium about joints (Dueasse ⁵⁰ -Tucker)		1022		N*		270		N	N		
Calcium following local infection (Pospelow ⁵⁰)	1045										
Epidermal calcification (Weldman and Shaf- fer ⁵³)	91 118					188	300	89		3 6	16
Subcutaneous calcification (Wilens and Derby)		N	N								
Metastatic calcification (Wells ⁴⁵)	†	†									

* "N" refers to a reported normal reading

† No figures available, thought to be increased (Wells, H G, personal communication)

LABORATORY OBSERVATIONS

Composition of Concretions — The concretions spontaneously extruded or excised from the cutaneous tissues have uniformly shown the presence of calcium phosphate and carbonate Hunter, ⁵⁷ Wildbolz ⁴⁰ and others recorded the presence of small amounts of magnesium also Uric acid and urates have always been absent, showing that the process is not related chemically to gout Quantitative determinations were not recorded Wells, however, found that the composition of most pathologic deposits of calcium salts in the calcified areas in the body seems to be practically the same if not identical, whether laid down normally

(ossification) or under pathologic conditions His analyses showed that the CaCo_3 varied from 10 to 15 per cent, and the $\text{Ca}^3(\text{PO}_4)^2$ from 85 to 90 per cent

Chemical Examinations of the Blood—In studying the chemical analysis of the blood in skin diseases, Pulay⁸⁶ found the calcium content high in two cases of scleroderma Gitlow and Steiner obtained low figures for the serum calcium in one case observed It is evident from table 1 that there is considerable variation in the serum calcium, even in the same type of case The figures are important mainly in showing that there is not constant oversaturation of the blood with the calcium salts in scleroderma, as there is supposed to be in metastatic calcification

COMMENT

Although combined cases of scleroderma and calcinosis are rare, the number of reported instances is sufficient to suggest that there is such a clinical and pathologic entity In Lewen and Heller's series there was an average of one case of the combined condition in every eighty-four cases of scleroderma reported In my series, the average is one case of scleroderma and calcinosis to every sixty cases of scleroderma It is true that it might be questioned whether these figures indicate more than a coincident relationship of the two conditions On the other hand, it is doubtful that x-ray examinations have been made in any large percentage of cases of scleroderma The close local relationship of the two conditions offers the strongest suggestion that they are not present by chance in the same person In several cases of calcinosis with localized scleroderma, the deposits were present only in the areas of skin sclerosis Furthermore, the deposits in the tissues of the phalanges, in cases of sclerodactylia and scleroderma involving the hands, seem fairly characteristic, although it is true that similar deposits, which followed local infections, are sometimes described without the accompanying skin condition It seems logical to conclude that there is a definite relationship between the two processes despite the infrequent occurrence

The priority of the appearance of the scleroderma or the calcinosis is not always made plain in the reported cases Even though the changes in the skin are not recognized in the early stage, in those cases in which priority is mentioned, the sclerosis of the skin usually antedated the recognition of the calcified nodules

Geographically, four cases are recorded to have occurred in England, three in France and six in the United States Most cases of uncomplicated calcinosis are reported in the literature of France and Germany

⁸⁶ Pulay, E Sklerodermie mit Sklerodactylie, Wien med Wchnschr **71**. 982, 1921

Deductions cannot be drawn from the ages of the patients. Two cases occurred in boys, aged 4 and 12. The only man in the group was 47, the recorded ages of the four other patients, women, were 36, 27, 38 and 64, respectively. The three cases with sclerodactylia occurred in women, whose ages were 34, 56 and 60. It is noteworthy that the time of onset in practically all of the cases in adults was early adult or middle life.

The concretions varied from small dots in the soft tissues around phalangeal joints to extensive areas of bone-like plaques, numerous deposits having become fused. The calcinosis was not limited to any single type of scleroderma, but occurred in most of the forms: the symmetrical, the generalized, the circumscribed (morphea) and the digital. No case of morphea guttata (white spot disease) was mentioned. The sclerosis of the skin likewise varied from involvement of a portion of the hands to generalized, widespread, symmetrical lesions.

Pathologically, the combined process does not differ from that of scleroderma, with the addition of foreign bodies scattered through the superficial or connective tissues. The epidermis is thin, with relative thickening of the horny layer. The fibrous layer of the dermis is thickened, and subcutaneous cellular tissue is replaced by a dense connective tissue, more dense in the deeper parts. The deposits of calcium are found mostly in the midst of the dense connective tissues, but may be more superficial.

All of the cases were under current clinical observation. No case had come to autopsy except the one reported by me. There seemed to be slow but definite progress of both types of lesions, particularly in older persons. Except in my case, the condition had not been a factor in a fatality; this case had progressed for thirty-seven years.

As the etiologic factor of scleroderma is by no means agreed on, and since opinions as to the causative mechanism of pathologic calcification are at such wide variance, ideas concerning the combination of these two conditions are even more puzzling. As is true in uncomplicated calcinosis, the variety of types and anatomic relationships add to the difficulty in arriving at conclusions that universally apply to all cases. For example, the question arises whether the small pleomorphic deposits in the phalanges, as seen in both Raynaud's disease and scleroderma, have the same etiologic factor, also whether the basic factor in their deposition is similar to that in cases with subcutaneous, periauricular and vascular involvement, which is sometimes extensive. The question also arises as to the relation or origin of such deposits without scleroderma. The cases in which the deposits are small and dotted predominate, and their presence raises a number of hypotheses about an alteration of the local metabolism of the skin and subcutaneous tissues, the process being more pronounced in scleroderma.

There are several mechanisms through which calcification might conceivably occur in association with the scleroderma (1) as a result of parathyroid dysfunction, (2) as metastatic calcification, (3) by simple chemical precipitation and (4) by means of a physicochemical disturbance in which colloidal proteins play a rôle

In experimental calcification, such as Hueper⁸⁷ and others produced by injecting parathyroid hormone, the deposits occurred most frequently

TABLE 2—*Recapitulation*

Sex	Age	Age at Onset	Location of Scleroderma	Location of Calcium Deposits	Accompanied by Sclerodactylia	Accompanied by Raynaud's Disease
Cases of Scleroderma with Calcinosis *						
F	36	Scleroderma 30	Extremities, elbows, knees, feet	In areas of scleroderma, in terminal phalanges and in larger tendons	Yes	Yes
F	33	Scleroderma 18 Calcinosis 21	Hands, lower part of arms, face, neck, back and buttocks	Phalangeal, metatarso phalangeal and regions of left elbow		Yes Onset at 14
F	27		Palmar surface of both hands	Phalanges and near olecranon	Yes	
M	47	Scleroderma 28	Both sides of face	In areas of scleroderma	No	Yes
M	4	3	Upper part of arms, shoulders and thighs	In area of scleroderma	?	Yes
F	64	57	Hands, feet, chest abdomen	In hands, olecranon and great toes	Yes	
M	12	?	Generalized	Both legs, arms and buttocks		
F	55	Scleroderma 42	Hands, arms, face and neck	Forearm, joints of both hands and left elbow	Yes	
F?	67	30	Legs and fingers	In areas of scleroderma, around many joints, widespread in cutaneous tissues	Yes	
Cases of Sclerodactylia with Calcinosis						
F	34	Scleroderma 4 Calcinosis 26		Fingers of both hands and at elbow		Yes
F	50	Scleroderma 35		Fingers and around left olecranon		
F	60	Childhood		Lateral and flexor surface of all digits		

* Details of two cases of scleroderma with calcinosis (reported by Delherm, Morel and Couput) were not supplied

in the excretory organs, the lungs, stomach and kidneys. The tissues of these organs are more alkaline because of their continuous excretion of acids. As the secretion from the sudoriparous glands is normally neutral or slightly alkaline, and since the interglandular tissues around the sweat glands are slightly acid after the alkaline secretion, the occurrence of deposits of calcium in the skin or subcutaneous tissues as a result of parathyroid disturbance does not parallel experimental observations. Histologically, too, there is a difference. In the experimental

87 Hueper, W. Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch Path 3 14 (Jan) 1927

type, the deposits of calcium were found in the interglandular tissues around the excreting glands, whereas in the reported cases, with cutaneous and subcutaneous involvement, the deposits were not in the interglandular tissues, but were scattered diffusely throughout the connective tissue

If parathyroid dysfunction is accompanied by histologic changes in the gland, such pathologic processes are rarely found. As before indicated, the parathyroid glands in my case seemed normal in histologic appearance.

An interesting corollary, however, is some recent work showing that the secretions of the thyroid and the parathyroid glands exert an antagonistic effect on each other, at least, several investigators have found that animals tolerate much more thyroid extract when parathyroid hormone is administered simultaneously. Since thyroid dysfunction is a frequent topic of discussion as a factor in scleroderma, and since parathyroid glands exert a regulatory influence on calcium metabolism, one might conjecture that there is a thyroid-parathyroid syndrome in the dual process.

The cases regarded as metastatic calcification present several essential differences from the collected cases of calcinosis with scleroderma. It is felt that the metastatic deposits may occur in tissues without demonstrable cell injury, whereas in the cases of scleroderma with cutaneous, subcutaneous or periarticular deposits, extensive vascular changes with alteration of the blood supply to the tissues and structural cell changes have been demonstrated. Rarefaction of skeletal bones is usually a constant occurrence in so-called metastatic calcification. In the cases of calcinosis with scleroderma there was no rarefaction, except osteoporosis resulting from disuse. In my case, the larger bones, particularly the calvaria, showed a marked increase in density. In none of the cases studied was there an oversaturation of the blood with calcium salts, as is thought to be a regular feature in the metastatic variety. The theory of metastatic calcification is incompatible, further, since this type of deposit is said to occur in places where the blood contains the least carbon dioxide. Obviously this condition is not present in the peripheral tissues. It seems unlikely, therefore, that the mechanism of calcification with scleroderma is similar to metastatic calcification.

Simple chemical precipitation of calcium salts occurs on the basis of alteration of the composition of the secretions, as is frequently seen in the cells and tubules of the kidney. As sweat contains a total of 0.57 per cent of inorganic salts, of which the alkali sulphates and phosphates comprise 0.18 per cent, and since the excretory function of the skin is definitely altered in scleroderma, the simplest conception would be that the normal excretory mechanism is sufficiently changed to cause calcium retention and local deposits.

Possible, but remaining to be proved, is the theory that as a result of sclerotic changes there is in or around the involved areas a local alteration of the normal p_H of the cells and tissue juices. With excretion diminished, these tissues would be expected to become more alkaline. It is known, too, that calcium salts are less soluble in an alkaline than in an acid medium, hence, precipitation might occur on the basis of a decrease of the solubility of the calcium salts in the tissue fluids or as a result of decreased solubility in the blood which flows through these altered areas. Obviously, these explanations do not throw any light on the numerous instances of deposits found in deeper tissues and around large and small joints not in areas of scleroderma. The frequent occurrence of cutaneous and subcutaneous deposits within sclerotic skin areas must, however, be of some significance.

Several observations have been made to determine whether the marked alteration of morphology and function of capillaries occurring in scleroderma would aid in determining what local chemical or metabolic disturbances result. Brown and O'Leary²¹ studied five so-called true cases of scleroderma, and found a quantitative deficiency of the capillary loops which roughly paralleled the trophic changes, they also observed many huge loops of increased length. Vasomotor phenomena were slight or absent. In five cases of the vasomotor type (Raynaud's disease with sclerodermatous changes), dilatation, stasis and disturbances of permeability were evident, to a great extent resembling the picture seen in true Raynaud's disease as described by Brown.⁸⁸ The disturbances of the skin were apparently secondary to the abnormal vasomotor reactions. Gitlow and Steiner also noted enlargement of capillaries and sluggish flow of blood. The venous ends were distended like bulbs. I have made similar observations. In a case of scleroderma involving the hands and arms, normal capillary function was first studied, subsequent studies were made after hypodermic injection of 2, 3 or 4 minims (0.123, 0.184 or 0.246 cc.) of epinephrine. Even 2 minims of this drug produced almost complete stasis in small capillaries, with pronounced slowing of the blood flow in the larger ones. The effect was fairly prolonged. The impression was gained from this one case that the effect of epinephrine seemed much more marked in the capillaries than was observed in normal controls. More careful subsequent studies are being planned with loop counts, diameter observations and records of the blood pressure. Should this observation be substantiated in other cases, the theory of endocrine influence as a factor in scleroderma may be strengthened further.

⁸⁸ Brown, G. E. The Skin Capillaries in Raynaud's Disease, *Arch. Int. Med.* 35:56 (Jan.) 1925.

These observations on the peripheral circulatory sluggishness seem most important, however, in connection with Hofmeister's⁶³ chemical observations previously quoted. It is his belief that as soon as a fluid in any way loses its free carbonic acid (for example, when the latter is bound to an alkaline medium), provided there is no increase in the velocity in the fluid flow or a higher protein content, a deposition of calcium phosphate can occur. These two observations do not permit final deductions, but may add a link in the chain of evidence.

Another likely possibility is that the colloidal proteins play a prominent rôle. Wells feels that the carbon dioxide in maximum concentration plus the effect of the colloids ordinarily prevents calcium deposition, unless the content of the blood calcium is much higher than normal. Hueper feels that the albuminous substances and the phosphates of the blood normally keep the calcium salts in solution and buffer greater changes in the p_H of the blood, thereby preventing precipitation of the calcium. He advances the hypothesis that a decrease in the amount of albuminous substances in the blood, as is found during nephritis (when considerable quantities of the blood albumin are excreted through the kidneys), offers a mechanism for the precipitation of calcium salts. Although such an explanation might fit in with the unusual degree of subcutaneous, vascular and periarticular calcinosis found in my case, in many other cases a history of heavy excretion of albumin or marked renal pathologic change was not emphasized. A further consideration is that the solubility of the calcium in the plasma is changed, although the amount of calcium in the whole blood is not above normal.

Thibierge and Weissenbach, after a detailed study of their case of scleroderma with sclerodactylia and calcinosis, felt that the elastic fibers did not play any part in the calcification, which they considered secondary to the formation of a more or less dense connective tissue, parts of which underwent a sort of colloid degeneration which favored the deposition of lime salts. This uncomplicated explanation, also favored by Jadassohn, may possibly be the most important factor in the process. No theory yet advanced, however, is sufficient in any way to explain why scleroderma and calcinosis are so infrequently associated. The lack of detailed histologic and biochemical information about the individual cases prevents more than speculative deductions. A further correlation of accumulated data by physiologists and physiologic chemists may aid in an explanation of the problem.

SUMMARY

1 Fourteen cases of calcinosis associated with scleroderma or sclerodactylia have been collected and added to the nine cases reported in 1911.

2 In four of the eight cases of scleroderma and calcinosis, there was an accompanying sclerodactylia. In three cases of sclerodactylia with calcinosis, there was no recognizable scleroderma.

3 The deposits usually appear subsequent to the changes in the skin, though they are sometimes seen unaccompanied by the trophic disorders of the skin

4 The calcinosis was not limited to any one type of scleroderma

5 The pathologic deposits of calcium vary from minute dots ("bony sand") to large fused areas, usually in the connective tissues but sometimes in the cutaneous tissues or extruding through the skin

6 Frequent anatomic sites of deposit were the soft tissues of the phalanges and the areas around the olecranon and elbow joints

7 Local inflammatory changes usually are not a causative factor

8 The usual composition of the deposits was calcium phosphate and carbonate. Uric acid was never found

9 Chemical studies do not indicate any constant variation in either the whole blood or the serum calcium values. There is no oversaturation of the calcium salts as is thought to occur in metastatic calcification

10 The calcinosis is unlike gout, true bone formations or calcium metastases

11 In one case with extensive generalized deposits of calcium, histologic evidence of a pathologic parathyroid process was not found at autopsy

12 That the combination of scleroderma and calcinosis constitutes a distinct pathologic entity, despite the infrequent occurrence, is suggested by the usual location of the calcinosis, by the fairly characteristic type of deposit and by the close local relationship of the two conditions (deposits usually in areas of scleroderma)

13 It is nowise clear whether calcinosis with scleroderma results from local metabolic alterations or deranged inorganic metabolism. As in other types of pathologic calcification, the colloidal proteins are thought to play a prominent rôle

THE BEHAVIOR OF THE PLASMA CHLORIDES IN OBSTRUCTIVE JAUNDICE*

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During the course of some observations on dogs after experimental obstructive jaundice had been produced, we were surprised at the frequency with which a reduction of the plasma chlorides occurred after complete obstruction of the duct and cholecystectomy in the same animal. The degree of reduction in the sodium chloride varied somewhat in different animals, but in all animals in which the obstruction was complete and in which the gallbladder had been removed, some depression in the amount of chlorides resulted. This behavior of the plasma chlorides may be, and probably is, only one part of an alteration in the entire physicochemical system of the animal, but it is most striking. The results here published are merely part of a more extensive study now being carried out.

In 1923, in a paper on "Observations on the Regulation of Osmotic Pressure," Gram¹ published some results of estimations on the plasma chlorides in human beings. In this work, he had further pursued the observation of himself and Norgaard² that a remarkable constancy of the ratio existed between the sodium chloride of the serum and the conductivity. In this further study, Gram included patients suffering from a number of diseases, among whom were several with jaundice. In his summary, he stated that

(a) Decreases of conductivity are due to changes in the salt content of the serum. This decrease occurs under two circumstances: (1) A primary decrease of salts with consequent low osmotic pressure in cases with simultaneous low salt intake and the formation of exudates and transudates, (2) a secondary decrease of salts tending to keep down the high osmotic pressure caused by an increase of non-electrolytes (sugar, urea, and gall constituents).

He presumed that jaundice belonged to the latter group.

In the animals used in our experiments, the degree of hyperbilirubinemia was estimated by the van den Bergh reaction. The stools were repeatedly examined for bile. At first, we had some trouble because of

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1 Gram, H. C. J. Biol. Chem. **56** 593, 1923.

2 Gram, H. C., and Norgaard, A. J. Biol. Chem. **56** 429, 1923.

reformation of the duct continuity This was thereafter prevented by oversewing the distal end of the duct with the omentum The reestablishment of the bile flow to the intestine resulted in a rapid decrease in the bilirubinemia and a rise in the plasma chlorides It will be seen

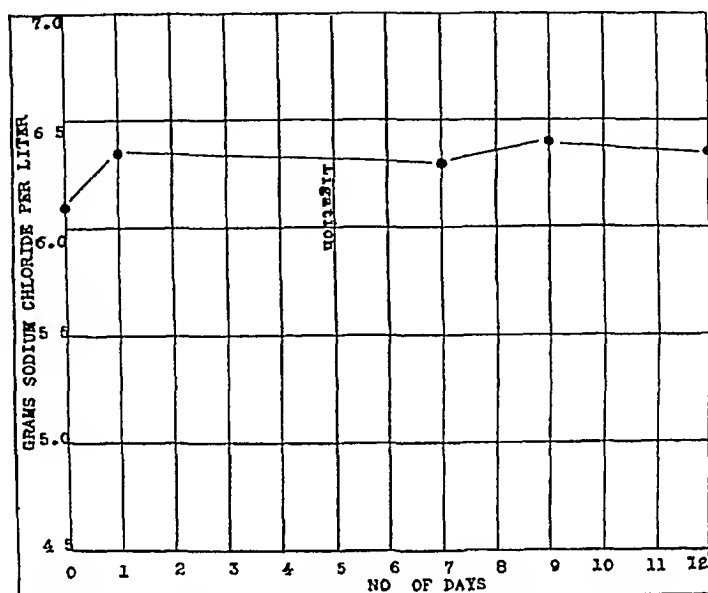


Chart 1 (dog 1) —Chloride values after simple ligation of the common duct

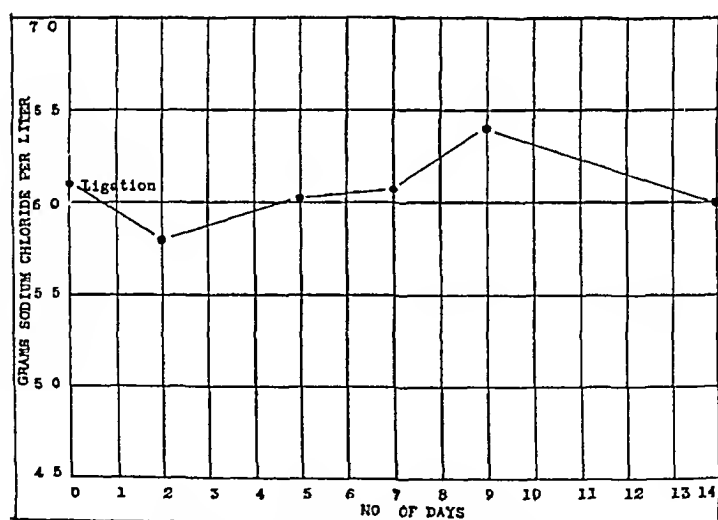


Chart 2 (dog 2) —Chloride values after simple ligation of the common duct

from the charts that an increase in the chlorides occurred at times even before a decrease in the blood bilirubin was ascertained

One of the most interesting features in this work was the behavior of the plasma chlorides in those cases in which the gallbladder was not removed at the time of ligation of the common bile duct In these cases, the only decrease in the plasma chlorides was that which might occur

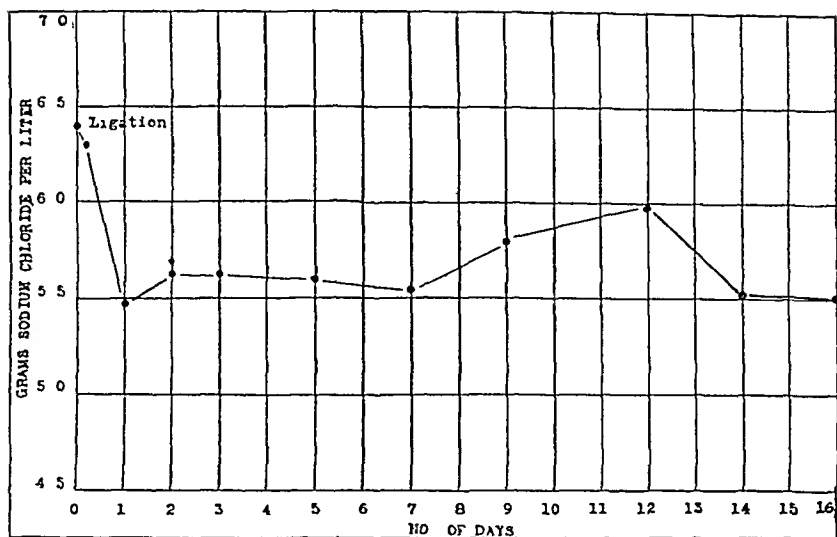


Chart 3 (dog 4) —Changes in the chloride plasma after ligation of both the cystic and the common ducts

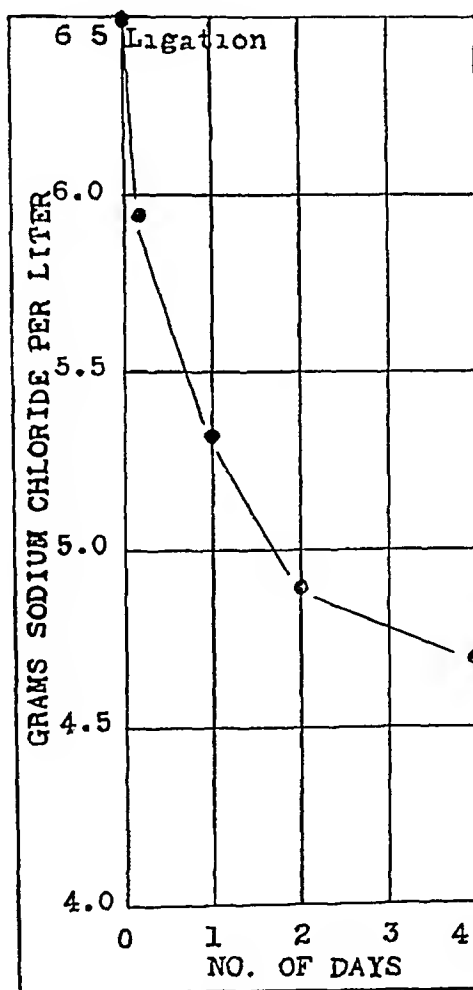


Chart 4 (dog 5) —Changes in the chloride plasma after ligation of both the cystic and the common ducts

immediately after operation That a decrease might be noted at a later stage of obstruction when jaundice had resulted is possible, but the behavior of the chlorides a few days after operation is entirely different from that after cholecystectomy and ligation of the common duct In another group of dogs, the gallbladder was removed, and the flow of bile to the duodenum was not disturbed Here, too, depression of the chlorides was not manifest In fact, although it may occur in the normal variation of plasma chlorides, in these cases the chlorides showed a tendency to increase

The accompanying charts illustrate the concentration of the plasma chlorides in grams of sodium chloride per liter, after three types of operations on the biliary tract of the dog The first group (charts 1 and 2) show the chloride values after simple ligation of the common

TABLE 1—*Concentration of Plasma Chlorides After Ligation of the Common Duct in Dogs in Group 1*

	Date	Sodium Chloride, Gm per 1,000 Cc	Van den Bergh	
			Direct	Indirect
Dog 1	10/ 6/26	6 11		
	10/ 7/26	6 35		
	10/11/26	Ligation of common duct		
	10/13/26	6 29		
	10/15/26	6 41		
	10/18/26	6 35		
	10/20/26	Reopened dog and explored region of common duct, found the common duct dilated and no other branch		
Dog 2	10/20/26	6 11		
	10/21/26	Ligation of common duct		
	10/22/26	5 78	Negative	Negative
	10/23/26	6 03	Negative	Negative
	10/27/26	6 07	Negative	Negative
	10/29/26	6 40	Negative	Negative
	11/ 3/26	6 00	Negative	Negative

duct They do not show any appreciable change Group 2 (charts 3, 4, 5, 6 and 7) give the changes in the chloride plasma after ligation of both the cystic and the common ducts In these, it will be seen that the amount of plasma chloride decreases, usually within twenty-four hours after operation, and continues to drop, remaining low as long as a hyperbilirubinemia exists The chlorides show a tendency to increase to within normal values even before a decrease in the bilirubinemia is manifest Group 3 illustrates the concentrations of the plasma chloride after cholecystectomy It will be seen that in these animals a depression of chlorides does not occur

The plasma chlorides were determined by the method of van Slyke,³ except in dog 15, in that case, the method of van Slyke and Donleavy⁴ was used

3 Van Slyke, Donald D J Biol Chem 58 523, 1923-1924

4 Van Slyke, Donald D, and Donleavy, John J J Biol Chem 37 551, 1919

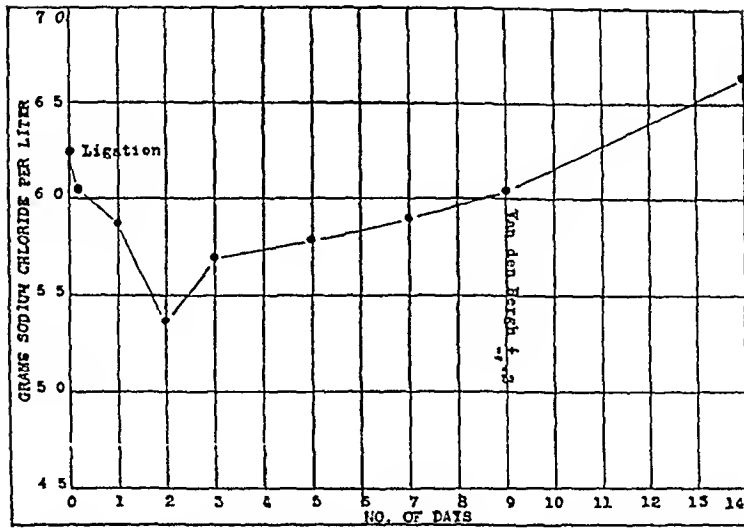


Chart 5 (dog 10) —Changes in the chloride plasma after ligation of both the cystic and the common ducts

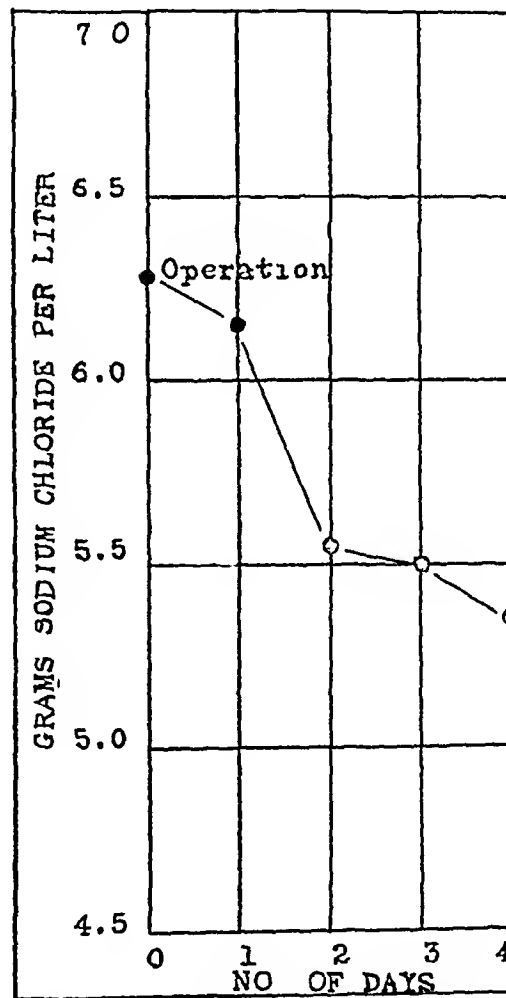


Chart 6 (dog 12) —Changes in the chloride plasma after ligation of both the cystic and the common ducts

TABLE 2—Concentration of Plasma Chlorides After Ligation of Both the Cystic and Common Ducts in Dogs in Group 2

	Date	Sodium Chloride, Gm per 1,000 Cc	Van den Bergh	
			Direct	Indirect
Dog 4	10/27/26, a m	6 41	Negative	Negative
	10/27/26, a m	Ligation of cystic and common ducts		
	10/27/26, p m	6 25	Negative	Negative
	10/28/26	5 49	Immediate	1 75 units
	10/29/26	5 63	Immediate	4 2 units
	10/30/26	5 63	Immediate	4 2 units
	11/ 1/26	5 59	Immediate	5 0 units
	11/ 3/26	5 56	Immediate	5 2 units
	11/ 5/26	5 84	Immediate	5 2 units
	11/ 8/26	5 97	Immediate	
	11/10/26	5 52	Immediate	5 0 units
	11/12/26	5 50	Immediate	
Dog 5	11/ 1/26, a m	6 50	Negative	Negative
	11/ 1/26, a m	Ligation of cystic and common ducts		
	11/ 1/26, p m	5 94	Immediate	1 15 units
	11/ 2/26	5 33	Immediate	1 75 units
	11/ 3/26	4 90	Immediate	2 25 units
	11/ 5/26	4 61	Immediate	4 50 units
Dog 10	12/ 1/26, a m	6 24	Negative	Negative
	12/ 1/26, a m	Ligation of cystic and common ducts		
	12/ 1/26, p m	6 09	Immediate	1 9 units
	12/ 2/26	5 88	Immediate	5 6 units
	12/ 3/26	5 36	Immediate	4 0 units
	12/ 4/26	5 72	Immediate	3 3 units
	12/ 6/26	5 81	Immediate	5 4 units
	12/ 8/26	5 90(stools black)	Immediate	4 6 units
	12/10/26	6 05 black)		
	12/15/26	6 64	Immediate	0 8 units
At autopsy, a small duct was found which allowed fluid to pass into the lower end of the divided duct, it was rather small				
Dog 12	12/19/26, a m	6 23		
	12/19/26	Ligation of cystic and common ducts		
	12/20/26	6 15		
	12/21/26	5 55		
	12/22/26	5 50		
Dog 15	12/23/26	5 35		
	6/29/27	6 56	Negative	Negative
	7/ 4/27	6 54	Negative	Negative
	7/ 5/27	Ligation of common duct and cholecystectomy		
	7/ 6/27	5 68		
	7/ 7/27	5 72	Immediate	3 4 units
	7/ 8/27	5 36	Immediate	3 5 units
	7/ 9/27	4 72	Immediate	3 5 units
	7/11/27	4 86	Immediate	

TABLE 3—Concentration of Plasma Chloride Cholecystectomy in Dogs in Group 3

	Date	Sodium Chloride, Gm per 1,000 Cc	Van den Bergh	
			Direct	Indirect
Dog 7	11/17/26	5 61	Negative	Negative
	11/17/26	Cholecystectomy		
	11/19/26	6 24	Negative	Negative
	11/22/26	6 29	Negative	Negative
	11/24/26	6 00	Negative	Negative
	11/26/26	5 74	Negative	Negative
	11/29/26	5 83	Negative	Negative
	12/ 8/26	5 99	Negative	Negative
	12/13/26	6 28	Negative	Negative
	1/ 5/ 7, a m	6 19	Negative	Negative
Dog 13	1/ 5/27	Cholecystectomy		
	1/ 5/27, p m	5 93		
	1/ 7/27	6 13	Negative	Negative
	1/ 8/27	6 08	Negative	Negative
	1/10/27	6 21	Negative	Negative
	1/12/27	6 11	Negative	Negative
	1/14/26	6 52	Negative	Negative
	1/19/27	6 46	Negative	Negative
	1/24/27	6 33	Negative	Negative
	1/ 7/27	6 00	Negative	Negative
Dog 14	1/ 7/27	Cholecystectomy		
	1/ 8/27	5 87	Negative	Negative
	1/10/27	6 28	Negative	Negative
	1/12/27	6 28	Negative	Negative
	1/14/27	6 39	Negative	Negative
	1/19/27	6 24	Negative	Negative

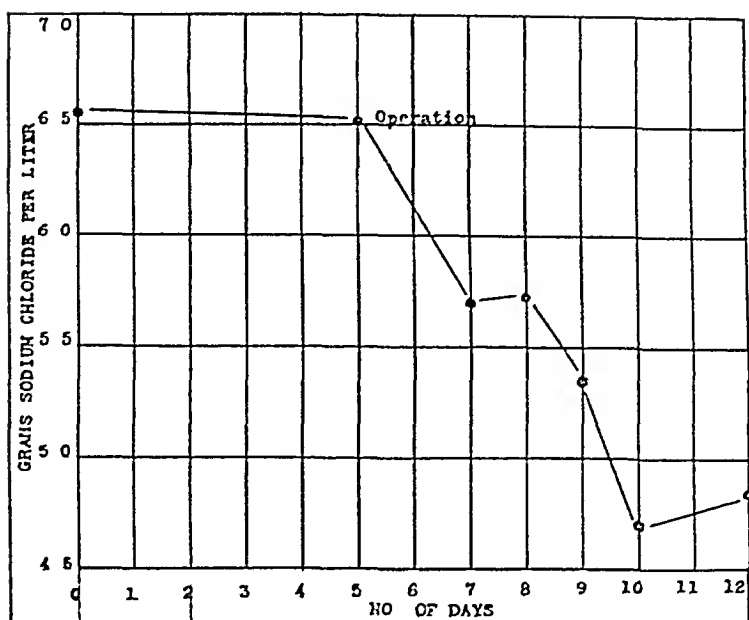


Chart 7 (dog 15) —Changes in the chloride plasma following cholecystectomy and ligation of the common duct

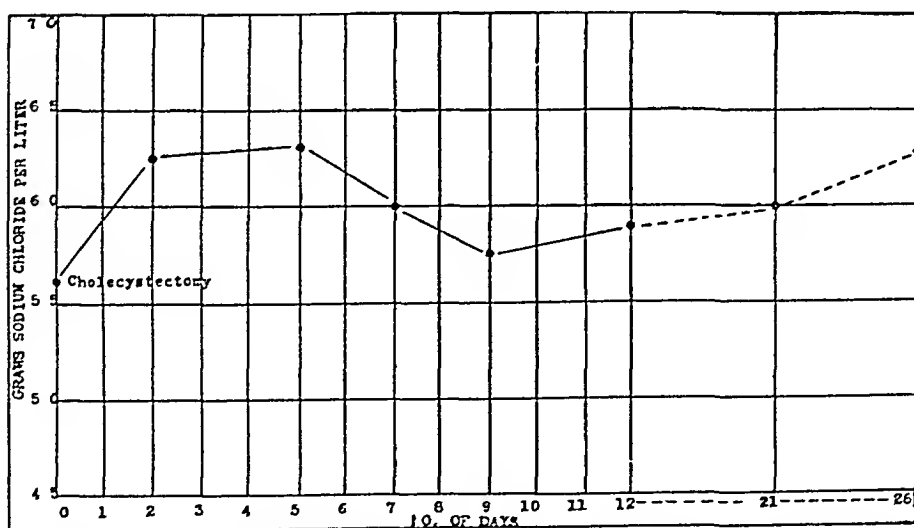


Chart 8 (dog 7) —Chloride values after cholecystectomy without ligation of the common duct

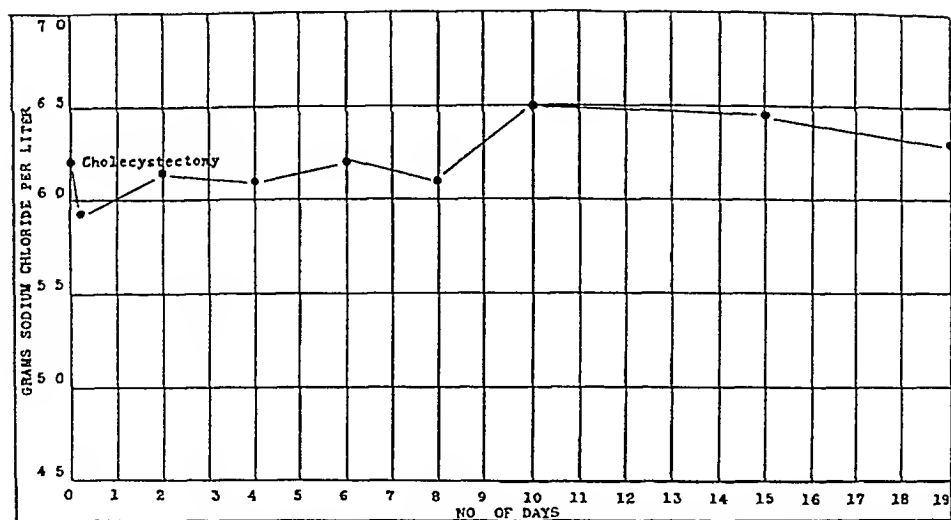


Chart 9 (dog 13) —Chloride values after cholecystectomy without ligation of the common duct

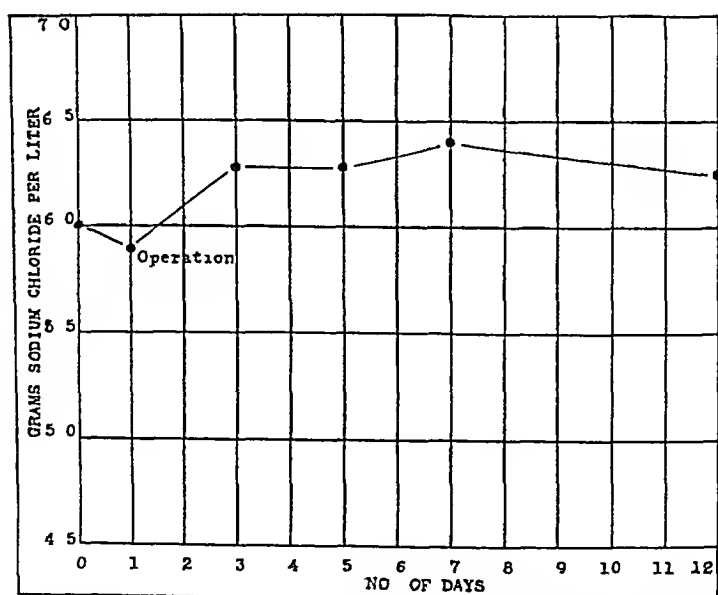


Chart 10 (dog 14) —Chloride values after cholecystectomy without ligation of the common duct

The importance of recognizing a depression of chlorides in patients suffering from obstructive jaundice is not definitely known. It may be that in the patient who is extremely ill, the restoration of the chloride which has been depleted would be attended by less operative risk. Recently, considerable emphasis has been placed on the administration of large amounts of fluid to patients before and after operation. In many of the patients so benefited, the improvement may be the result of restoration of the sodium chloride lost during depletion.

Whether the depression of plasma chlorides which we have observed is the result of an attempt at osmotic compensation or still other factors, remains in doubt. N₁⁵ recently reported an increase in the blood sugar which accompanied a primary depression of the chlorides. In obstructive jaundice, a rise in the blood sugar values has not been found in our animals, even though the chloride depression has been marked, so that the inverse ratio, as N₁ calls it, between dextrose and chloride does not exist in these cases. We believe that, besides an attempted osmotic compensation, the gallbladder itself may play some part in the chloride metabolism after obstructive jaundice.

SUMMARY

Data are presented concerning the chloride metabolism after ligation of the common duct (group 1), cholecystectomy and ligation of the common duct (group 2), and cholecystectomy alone (group 3). In groups 1 and 3, depression of plasma chlorides was not found. In group 2, a reduction in the plasma chlorides occurred, varying in degree but consistently present whenever ligation was complete and the gallbladder out of the circuit.

5 N₁, T. G. *Am. J. Physiol.* **78**: 158, 1926.

BRONCHOMONILIASIS

REPORT OF A CASE FROM PORTO RICO *

W R GALBREATH, M D

AND

CHARLES WEISS, M D

PORTO RICO

Bronchomoniliasis was first described as a disease entity by Castellani¹ in 1905, while he was working in Ceylon. The disease has since then been observed in various tropical, subtropical and temperate regions. Cases have been reported from India, South Africa, West Africa, Soudan, Egypt, the Belgian Congo, South America, France, southern Italy and England. Boggs and Pincoffs² also published records of a case from Baltimore.

ETIOLOGY

Castellani and Chalmers stated that bronchomoniliasis is generally due to *Monilia tropicalis* in Ceylon, South India and the Malay States. They expressed the opinion that the fungus is the real cause of the disease, since no other etiologic agent, such as the tubercle bacillus, is found. Moreover, when the condition improves, the fungus becomes scanty or disappears completely. Castellani³ also described other non-pathogenic species of *Monilia* in chronic bronchitis. These species are *M paratropicalis*, *M pinoy*, *M krusei* and others. We have found *Monilia psilosis* (*ashfordi*) in a case originating in Porto Rico.

Under the term *Monilia* is included a genus of microscopic plants belonging to the class of *Hyphomycetes* or "fungi imperfecti," the vegetative body or thallus of which appears in the lesions in the tissues (i.e., in its parasitic life), as a mass of mycelial threads or free-budding forms, some of the mycelial filaments are long and branched and often present arthrospores. An investigation of the biochemical characteristics of *Monilia* shows that it often ferments dextrose and other carbo-

* From the Presbyterian Hospital, San Juan, Porto Rico, and the School of Tropical Medicine of the University of Porto Rico, under the auspices of Columbia University.

1 Castellani, A. Hemorrhagic Bronchitis of Non-Tubercular Origin, Proc Internat Conference on Health Problem in Tropical America, Boston, United Fruit Company, 1924, p. 857.

2 Boggs, T. R., and Pincoffs, M. C. A Case of Pulmonary Moniliasis in the United States, Tr. A. Am. Phys. 30: 474, 1915.

3 Castellani, A., Douglas, M., and Thompson, E. Notes on Mixed Mycotic Infection of the Bronchi, Mixed Monilia and Anaeromyces Infection, J. Trop. Med. 28: 257 (July) 1925.

hydrates with the production of acid and gas, and on the basis of these characteristics *Moniliae* have been classified by Castellani into several groups. It may be pointed out that *Moniliae* which present the same biochemical properties may differ enormously as regards pathogenicity, some produce a severe infection when inoculated into the rabbit or guinea-pig, while others appear to be harmless.

In recent years, there has been a widespread interest in the study of *Monilia* in relation to chronic diseases of the respiratory tract. Many types of yeastlike organisms have been isolated from the sputum of patients with chronic bronchitis and asthma by various investigators, particularly Kotkis, Wachowiak and Fleisher⁴ of St. Louis and Steinfield⁵ of Philadelphia. Relief from symptoms was obtained in many of these patients by treatment with autogenous monilia vaccines. The investigators from St. Louis assumed that "the monilia are secondary or concomitant factors, although possibly they may be the chief ones in maintaining the chronicity of the symptoms. It is possible that some irritant agent, bacterial, toxic or mechanical, may initiate in the mucosa of the bronchus certain changes as a result of which the monilia are now able to grow and maintain their existence here." At present, however, there is no agreement among writers as to what constitutes the genus *Monilia* and as to whether it has a primary or merely secondary rôle in the etiology of nontuberculous chronic bronchitis.

SYMPTOMATOLOGY

Mild, intermediary and severe types of the disease are described by Castellani. The symptoms in general are dyspnea, cough, expectoration, with or without blood, and fever. The disease is characterized by frequent remissions and exacerbations. During the periods of remission, the fungus grows less or may entirely disappear from the sputum.

In the mild type, the patient looks well and complains of a slight cough. The expectoration is mucopurulent, yellowish, greenish or whitish and often scanty, without blood. The disease may end spontaneously within a short period or last longer, remaining stationary or passing into the severer types.

In the intermediary type, the patient complains of more or less severe cough and dyspnea, and not infrequently of subcontinuous fever. The cough comes in paroxysms and is worse in the morning and at night than in the daytime. Cries of severe hemoptysis rarely occur. Fever is

4 Kotkis, A. J., Wachowiak, M., and Fleisher, M. S. Relation of *Monilia* to Upper Air Passages, *Arch. Int. Med.* **38**: 217 (Aug.) 1926.

5 Steinfield, E. Bronchomycosis Associated with Certain Types of Bronchial Asthma, *J. A. M. A.* **82**: 83 (Jan. 12) 1924, A Study of the Yeast Found in the Sputum of Patients with Asthma and Chronic Bronchitis, *J. Lab. & Clin. Med.* **8**: 744 (Aug.) 1923.

usually absent although at times there is a subcontinuous or continuous fever. Bodily nutrition may be well maintained. The physical signs of the chest are the same as in chronic bronchitis.

The severe type of the disease runs a chronic course and almost invariably ends fatally. One or both lungs may be affected, and the pleura is frequently involved. There is cough, expectoration of blood and hectic fever. The appetite is bad and the patient looks emaciated. The course of the disease closely resembles that of tuberculosis. The physical examination of the chest reveals patches of dulness due to consolidation and pleural thickening, bronchial breathing, diminished or entirely absent vesical murmurs, crepitations, pleuritic friction sounds, and later, signs of cirrhosis of the lungs with its sequelae.

DIAGNOSIS

The diagnosis of bronchomyciasis is based on the constant finding of a pathogenic species of *Mompha* in the expectoration of the patient. It is difficult to rule out the significance of various bacteria such as the pneumococcus, streptococcus and staphylococcus which are commonly present in the sputum. By the method of Bull and Tao,⁶ it may be shown that *Mompha* will grow better in the blood of the patient than in normal controls (Weiss and Landrón⁷).

The sputum, collected after thorough rinsing of the mouth with an alkaline antiseptic solution, should be placed in a sterile Petri dish. Occasionally, *Mompha* may be seen by direct microscopic examination, usually it is best to streak the sputum (after washing it with sterile saline) over the surface of a Sabouraud dextrose agar plate, pH 6.5, and to incubate at 35 C for from one to four days. One should look for rather large creamy white opaque colonies. By means of the low power objective (1/6) the colonies of *Mompha psilosis* may be seen as coarsely granular, resembling a mosaic of tiny glass marbles.

A pure colony should be transplanted to various carbohydrate mediums in fermentation tubes and into gelatin and litmus milk. Most *Momphae* do not ferment lactose, mannite, dulcitol, dextrin, the various vegetable starches or glycerin. The characteristics of *Mompha psilosis* (*ashfordi*) are given under the heading "Cultural Studies."

Intravenous injections should be made into the lung of rabbits to see if the strain of *Mompha* is pathogenic and capable of producing pulmonary lesions. Many saprophytic *Momphae* may be encountered, these

6 Bull, C. G., and Tao, S. M. A Method for Determining the Anti-Pneumococcal Properties of Whole Blood and the Protective Power of Immune Serum, *Am J Hyg* 7:648 (Sept.) 1927.

7 Weiss, C., and Landron, F. Immunological Studies of Tropical Sprue in Porto Rico, *Am J Trop Med*, to be published.

do not have any etiologic relationship to bronchomoniliasis. Intravenous injections of other species of *Monilia* may kill rabbits, but fail to produce pulmonary lesions, hence, these are considered to be merely secondary invaders. The species of *Monilia* is considered by Castellani to be the real causative agent when it produces in rabbits (on injection into the lung) a number of small pulmonary nodules showing endothelial proliferation, giant cells and *Moniliae*.

Primary bronchomoniliasis should be differentiated from the secondary type not infrequently met with in cachectic disease such as cancer, tuberculosis and diabetes. In these cases the mucous membranes of the mouth, pharynx, larynx and bronchi are covered with the fungus, whereas in genuine bronchomoniliasis the mouth and pharynx are not affected. It should be differentiated from tuberculosis by the absence of the tubercle bacillus in the expectoration, and by the negative results from inoculations into animals, from bronchopneumocystosis and endemic hemoptysis by the absence of spirochetes and ova of *Paragonimus westermani*.

Prognosis is favorable in the mild cases, the intermediary types are chronic and difficult to cure, and the severe types, as a rule, end fatally.

TREATMENT

Potassium iodide is considered to be the specific in this disease, and patients with mild cases often recover with its use. Doses of from 0.5 to 1.5 Gm., well diluted in water or milk, are given three times daily. In severe cases the drug is useless.

In connection with the use of potassium iodide, creosote and tonics, especially phosphoric and arsenical compounds, the question of nourishing food and residence in suitable climate should never be neglected. Vaccine therapy may be tried. Farah⁸ obtained excellent results from the use of intramuscular injections of 2 cc. of a solution of iodized oil 40 per cent—into the gluteal region of his patients on alternate days, as many as forty injections were given without any signs of iodism. Patients with the mild and intermediary types of the condition were greatly benefited. This treatment appears to be useful in early cases before any serious damage has occurred to the lungs.

REPORT OF A CASE

History—G. A. S., an American man, white, aged 34, married, a clerk in a stationery store, had lived in Porto Rico twelve years. He was admitted to the Presbyterian Hospital on April 23, 1926, complaining of pain in the chest, night sweats, persistent cough in the mornings with occasional expectoration of blood-

⁸ Farah, N. Observations on Castellani's Bronchomoniliasis, *J. Trop. Med.* 26:1 (Jan.) 1923.

tinged sputum, frequent headaches, occasional attacks of diarrhea alternating with constipation, and daily fever. During the war, he had been in the military service in Porto Rico and had suffered from a severe attack of influenza. In 1918, when discharged, he was in a poor physical condition and complained of cough, pain in the chest, shortness of breath, fever in the afternoon and night sweats. His condition was diagnosed as tuberculosis, and he went to a local sanatorium where he spent six months, most of the time in a recumbent position. He made little improvement in his general condition during this treatment and showed a daily rise in temperature. During the interval between 1918 and 1926, numerous examinations of the sputum were made for tubercle bacilli, but evidence of the bacillus was never found. The diagnosis of tuberculosis was made in this sanatorium on the basis of physical observations and roentgen-ray examinations.

The patient had had measles, whooping cough, chickenpox and diphtheria during childhood, typhoid fever had occurred at the age of 12 and malaria some time later. He had had influenza in 1917. He said that he had not had any venereal infections.

Physical Examination—The patient was in a good state of nutrition. Examination of the chest revealed rough breathing below the angle of the right scapula and some roughness of the breath sounds at the end of inspiration in the left infraclavicular area close to the sternum. The percussion note was impaired over the upper and middle lobes of the right lung and slightly impaired over the apex of the left lung. Just below the right clavicle moist bubbling râles were heard which disappeared after coughing, but returned promptly. Bronchovesicular breathing was heard below this area. The heart was somewhat enlarged, the apex being at the sixth interspace in the anterior axillary line. Rhythm and tone were regular, murmurs were not noted.

During the two weeks of observation in the hospital, the patient's temperature was usually about 99 F, but on a few occasions it rose as high as 100.4 F. The pulse rate fluctuated from 60 to 90, and the respirations were usually about 20 per minute. The patient's weight on admission was 141.5 pounds (64.0 Kg) and was the same when he left the hospital.

Since his discharge from the Presbyterian Hospital in 1926, the patient has been under observation in the clinic. He has continued his work and has refused to take any medical treatment. About two months prior to presentation (Jan 27, 1928), he had had an attack of hemoptysis. Laboratory and roentgen-ray examination still failed to reveal any evidence of tuberculosis. *Mouths* were present in abundance in the sputum.

Laboratory Examination—Urinalysis revealed an acid reaction, specific gravity, 1.027, and an absence of albumin, sugar and casts, and abnormal constituents in the sediment.

Examination of the feces on April 23, 1926, showed *Trichuris trichiura* eggs to be present, an examination on June 7, 1927, revealed *Monilia psilosis* isolated on Sabouraud dextrose agar plate.

Examination of the blood on April 23, 1926, showed red blood cells, 4,400,000, white blood cells, 8,100, hemoglobin, 80 per cent, polymorphonuclears, 70 per cent, mononuclears, 30 per cent.

An examination on April 29 showed white blood cells, 9,700, polymorphonuclears, 64 per cent, eosinophils, 9 per cent, mononuclears, 24 per cent, transitionals, 2 per cent.

Examination on Jan 26, 1928, showed red blood cells, 3,300,000, white blood cells, 7,800, hemoglobin, 70 per cent (Dare), polymorphonuclears, 66 per

cent, small lymphocytes, 30 per cent, large lymphocytes, 2 per cent, and transitionals, 2 per cent (100 white blood cells counted)

A chemical examination of the blood on May 27, 1927, revealed sugar, 125 mg per hundred cubic centimeters, urea nitrogen, 7 mg per hundred cubic centimeters, uric acid, 42 mg per hundred cubic centimeters, creatinine, 15 mg per hundred cubic centimeters

Bacteriologic examination of specimens of sputum taken at daily intervals for one month (from May 7, 1926, to June 5, 1926) were negative for tubercle bacilli. On June 10, 1927, several specimens were again examined by the direct and antiformin methods and found negative for tubercle bacilli. Cultures of the sputum on Lubenau's medium were also negative. Pneumococci, streptococci and staphylococci were isolated. Dark-field examination did not reveal any spirochetes.

Cytologic examination of the sputum revealed large round cells and also much mucous and bronchial epithelium, a few red blood cells and white blood cells were seen.

Mycologic examination of the sputum using Sabouraud agar gave several colonies of *Monilia psilosis* on numerous occasions. On June 20, 1927, specimens of the patient's sputum, treated with antiformin, were inoculated into two guinea-pigs. They did not show any signs of tuberculosis for four months. On June 24, 1927, 2 cc of a saline emulsion made from a three day old culture of *Monilia psilosis* isolated from the patient's sputum was injected intravenously into a rabbit. The animal died on the sixth day.

Postmortem examination revealed congestion of the lungs and large white kidneys. *Moniliae* were isolated from these organs.

Microscopic examinations of the tissues of the animal were made by Dr R. A. Lambert, Professor of Pathology, and Director of the School of Tropical Medicine of the University of Porto Rico. He reported as follows:

"Acute destructive inflammatory foci are found in the lung, kidneys and tongue. The lung shows a widespread oedema, small poorly defined foci, with necrosis and polynuclear infiltrations in the center surrounded by a zone in which there is mononuclear infiltration and epithelial and connective tissue proliferation. The kidney shows more marked inflammatory changes, though quantitatively like those in the lung. In some of the suppurative foci clumps of yeast-like structures are easily recognized by their pale basic stain, well defined cell membrane and double contour. Many of the tubules are filled with pus. Proliferative changes are marked. The liver presents fatty changes of moderate degree, but no focal inflammatory lesions. The spleen and heart are negative. The section of tongue includes a small area of ulceration covered by a membranous exudate.

Diagnosis. Acute focal inflammatory lesions of tongue, lung and kidney (Experimental Moniliasis).

On Jan 20, 1928, the patient coughed into a Petri dish containing Sabouraud medium. A few colonies of *Monilia* were found. On Jan 26, 1928, the patient expectorated a thick viscid sputum with much visible blood. Microscopically, a mass of leukocytes and red blood cells were seen embedded in mucus. Tubercle bacilli could not be demonstrated by either direct smear or the antiformin methods. The results of inoculation into guinea-pigs for tubercle bacilli were negative. (The animals were observed for three months.)

Cultural Studies—*Moniliae* which we isolated conformed in every way to the description given by Ashford. The latter corroborated our mycologic observations in this case. The colonies on Sabouraud dextrose agar were thick cream-colored.

If cultivated for several weeks on the surface of a Sabouraud slant, the culture assumed the appearance of a cameole with delicate arborizations extending into the substance of the medium

Yeastlike oval forms were readily found in young as well as in old cultures These had a definite capsule containing hyaline plasma with a vacuole containing one or more actively motile bodies Mycelial threads were obtained by digging into the agar with the platinum loop, these presented subdivisions by means of septums and often motile bodies Budding cells were also seen

The following is a summary of the behavior on various mediums In Sabouraud dextrose agar (pH 6.5), there were typical, creamy elevated colonies In gelatin there was no liquefaction, an inverted pine tree was present In litmus milk, there was no coagulation and the medium became progressively more alkaline In dextrose, maltose, d-mannose or raffinose broth, acid and gas were produced Acid production was delayed in saccharose and galactose and acid in xylose broth There was no liquefaction in Loeffler's coagulated beef serum In Russel's double sugar the butt was slightly acid, the slant, alkaline In lead acetate agar, the butt was negative, the slant showed brown discoloration The organism grew well in a J Howard Brown anerobic jar, and produced active fermentation of maltose under a petrolatum seal

Roentgen-Ray Examination—A roentgen-ray examination on Nov 27, 1922, by Dr. Roses Artau, showed the right pulmonary shadow excessively accentuated The glands were enlarged, there was nuclear condensation There was possible apical pleurisy on the right side

On March 31, 1923, both apexes were slightly less transparent There were increased hilum shadows with diffuse infiltration of both lungs

On Sept 19, 1923, there was slight infiltration of both apexes and increased hilum shadows The peribronchial nodes were calcified

On June 23, 1925, the bases and apexes were normal The hilum shadows had increased, and there was slight fibrosis with discrete mottling

On Dec 28, 1925, there was slight mottling of the median lobe of the right lung

The last examination on Jan 27, 1928, was taken during a period of exacerbation of the patient's symptoms, while he was in poor general health and suffering with daily afternoon rise in temperature and expectorating a thick viscid sputum containing much free blood and many cells and *Monilia* There was extensive peribronchial infiltration with apparent calcification of glands near the hilum The parenchyma was mottled throughout both bases with several small abscesses in the middle lobe of the right lung There was a marked thickening of the pleura on the left side The apex of the left lung was clear, the right was slightly cloudy The heart shadow was slightly increased

SUMMARY

A case of pulmonary moniliasis is reported occurring in a white American man, who has been living in Porto Rico for twelve years The symptoms simulate chronic pulmonary tuberculosis, but repeated examinations of the sputum over a period of ten years by direct microscopic and antiformin methods as well as by animal inoculation have failed to show the presence of tubercle bacilli On the other hand, there is always present in the sputum a yeastlike organism of the genus

Monilia psilosis (ashfordi), which is pathogenic for guinea-pigs and rabbits, and produces necrosis of the lung with mononuclear infiltration and connective tissue proliferation on intrapulmonary injection into rabbits. These animals usually die within six days and show a general moniliasis with inflammatory lesions of the tongue, lungs and kidneys.

These laboratory observations together with the results of the roentgen-ray examinations and the clinical history of the case lead us to regard this as a case of bronchomoniliasis. That *Moniliae* are the primary cause of the disease and not secondary invading organisms which contribute to the chronicity of the disease and its toxic symptoms has not been absolutely proved.

SOME OBSERVATIONS ON THE SCAPULAE OF THE CHINESE *

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In 1906, Graves began his observations on scapular types and their relation to morbidity in the individual subject. Since then, in numerous papers he¹ has presented the results of his studies, which include a classification of scapulae according to their vertebral borders, as convex, straight and concave. The last two types he grouped together and called scaphoid. In them, he found that the bone is longer, the inferior angle more acute and the spine more horizontal. The classification of scapulae according to age periods showed a striking decrease in the incidence of the scaphoid type as old age was approached. This he explained as due either to a change from the scaphoid to the convex type, as the individual grew older, or to a greater mortality among those with the scaphoid type of scapula. Examination of the scapulae of the fetuses showed definite types as early as the tenth week, and repeated observations on persons over periods of years did not disclose any change in the individual scapular form. This convinced Graves that the scapular characteristics for persons do not vary with age, and that the scaphoid type of bone is an indication of increased susceptibility to disease and occurs among those he calls the "potentially sick" of the race. According to Graves, scapular forms are hereditary, and are an indication of longevity and of morbidity in general. At one time, he thought that the scaphoid scapula might be an indication of syphilis in the ascendants, and a sign of general degeneration.

The investigations of Warburg,² Cunningham,³ Kollert,⁴ Chotzen⁵ and others confirm the observations of Graves concerning the frequency of scaphoid scapulae in general and its decreasing frequency in the

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1 Graves, W W. *J Cutan Dis* **31** 241, 1913. The Relations of Scapular Types to Problems of Human Heredity, Longevity, Morbidity and Adaptability in General, *Arch Int Med* **34** 1 (July) 1924, Methods of Recognizing Scapular Types in the Living, *ibid* **36** 51 (July) 1925, The Plus-Potentially Sick of the Race, Glasgow, Alexander Macdougall, 1925, The Relation of the Shoulder Blade Types to Problems of Mental and Physical Adaptability, London, Oliver & Boyd, 1925.

2 Warburg. *Med Klin* **9** 1851, 1913, *Klin Wchnschr* **2** 31, 1919.

3 Cunningham, R L. The Scaphoid Scapula, *Arch Int Med* **10** 589 (Dec) 1912.

4 Kollert. *Wien klin Wchnschr* **24** 1299, 1911.

5 Chotzen. *Klin Wchnschr* **55** 949, 1918.

succeeding age periods. Regarding the question of interpretation, however, some writers, especially Warburg and Cunningham, do not agree. They are of the opinion that the scaphoid scapula is simply a normal variation from the usual convex type. It is interesting to note that these observers examined persons in only one age period (Warburg from 6 to 7 years, Cunningham from 16 to 25 years) and could not find any signs of degeneration, either physical or mental, in persons with scaphoid scapulae when compared with those with convex scapulae. Cunningham's observations were made on college and university students, and she feels that if there is any difference in mental capacity between those having convex and scaphoid types, the advantage is in favor of the latter.

There does not seem to be any doubt about the existence of a progressive decrease in the incidence of scaphoid scapulae in succeeding age periods and, as Graves says, there can be only two possible explanations: either the scaphoid type is converted into the convex type, or many of the scaphoid group are eliminated through death. He believes that there is evidence to show that the scapular type is determined early in fetal life and probably continues without change in type throughout the life of the person. Curtius,⁶ on the other hand, states that his observations support the view of change of the scapular form, in that he found relatively few scaphoid forms at birth and a rapid increase in incidence with advancing age, followed by a falling off again as adult life is reached. He feels that rickets and muscular pull determine the type, except for the rare congenital cases. Those with scaphoid scapulae also showed other stigmas of rickets. Regarding muscular pull, he believes that if the infraspinatus—subscapularis—serratus anterior group is stronger than the rhomboid group, the concave type will result, if they are equal, the straight type will predominate, whereas, if the rhomboids are the stronger, a convex border will result. Granting that this explanation is correct, there is still the fact of the decreasing incidence of scaphoid scapulae with each decade of life to explain. Unless there is a change in the form of the scapular vertebral border after adult life, which is scarcely conceivable, there must be a higher rate of mortality among bearers of the scaphoid type.

In order to determine the occurrence of scapular types and their incidence among the Chinese, observations were made on 546 persons ranging from 15 to 78 years of age. The observations were made according to Graves' method of palpation. In a large number of cases, roentgenologic examinations were made for confirmation. These were made only on adults, however, in order to be sure that the vertebral border was ossified.

6 Curtius, F. *Deutsche Ztschr. f. Nervenheilk.* **92** 101, 1926

Of the 546 cases, 258 or 47.2 per cent of the subjects had convex scapulae, 194, or 35.4 per cent, had straight scapulae, and 94, or 17.4 per cent, had concave borders. Convex scapular vertebral borders were, therefore, found in 47.2 per cent of the cases compared with 52.8 per cent of the scaphoid type. Examinations were not made of persons under 15 years of age. According to age periods, there was an extremely definite drop in the incidence of the scaphoid type with each decade, as is shown by the accompanying table. There was not only a decrease in the frequency of the concave type but also a decrease definitely in the straight type.

In classifying the scapulae observed, it was found that 94, or 17.4 per cent, were of the mixed type and were practically always either convex and straight or concave and straight, only 3 being combined convex and concave. In these cases, those with one convex scapula were classified as convex, and those with one concave scapula were classified with the concave.

Age Incidence of Scaphoid Scapulae

Age	Convex, Per Cent	Scaphoid, Per Cent
15-20	17.9	82.1
21-30	41.5	58.5
31-40	47.3	52.6
41-50	63.0	37.0
51-60	72.7	27.2
60 +	84.6	15.4

One hundred and ninety-two of the 546 persons examined had Wassermann and Kahn tests of the blood, and of these the tests for only 16 were positive. Ten of the 16 positive reactions occurred in patients with convex scapulae and 6 in patients with scaphoid scapulae.

Of 305 persons whose lungs were found normal by roentgen-ray examination, 55 per cent had scaphoid scapulae. Fifty-two per cent of 109 cases diagnosed as pulmonary tuberculosis were shown by roentgenologic examination to be present in patients with convex scapulae. From these observations on the pulmonary conditions of 414 persons, it does not seem justifiable to say that, in general, persons (Chinese) with scaphoid scapulae are more susceptible to pulmonary tuberculosis than are other persons.

The etiology of scaphoid scapula was not brought out by these observations, but the progressive decline in the percentage of the scaphoid type of scapula with each succeeding decade of age seems definitely to indicate a greater mortality among persons with this type of scapula. It seems inconceivable to me that there can be a change in the shape of the bone after maturity has been reached.

There was nothing in these observations to indicate degeneracy among persons with scaphoid scapulae.

SUMMARY

Five hundred and forty-six Chinese were observed for scapular types

A definite decrease in the incidence of scaphoid scapula with each succeeding decade of life was found, which is interpreted as indicating an increased mortality among persons with scaphoid scapulae

No relation was found between scaphoid scapula and syphilis in the individual as revealed by the Wassermann and Kahn reactions

The absence of pulmonary tuberculosis was just as frequent among bearers of scaphoid scapulae as among those with the convex type of scapula, and conversely, pulmonary tuberculosis was as frequent in persons with convex scapulae as in those with the scaphoid type of scapula

THE ELECTROCARDIOGRAM IN HYPERTENSION

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Chronic disease of the heart muscle, often called "chronic myocarditis," is the most common type of heart disease found in patients after the age of 40. Hypertension, which is present in about 75 per cent of the cases, is believed to be the most constant and the most important factor in causing this condition. The changes produced in the heart muscle as a result of hypertension are not always recognized clinically, and often it is only through electrocardiographic examination that the condition is detected.

To determine the significance, therefore, of the electrocardiographic observations in hypertensive heart disease, a study was made of 100 consecutive patients with hypertension who presented themselves for treatment at the heart clinic of the medical dispensary of the University of Minnesota. A thorough physical examination, a roentgen-ray examination and an electrocardiographic examination were made in each case.

In 37 of the cases (37 per cent), abnormal signs were not noted in the electrocardiogram. According to the roentgen-ray examination, the heart was normal in size in 21 of the 37 cases and enlarged in 16 cases. The enlargement varied from a slight degree in 12 to a marked degree in 4 cases. The blood pressure was 200 or over in 13 of the 21 patients with normal sized hearts, and 8 had a pressure under 200, 8 of the 16 patients with enlarged hearts had a blood pressure of 200 or over.

Sixty-three of the 100 patients showed some abnormality in the electrocardiogram. Extrasystoles were noted in 12 cases. These were divided as follows: auricular, 1, nodal and auricular, 1, interpolated, 1, right ventricular, 4, left ventricular, 4, and right and left ventricular, 1. In 6 of the 12 cases with extrasystoles signs of myocardial damage were noted, such as negative T waves in leads I and II, delayed conduction, etc.

A delay in conduction was noted in 5 of the abnormal cases. In 3 cases there was a delayed intraventricular conduction, in 1 a delayed auriculoventricular conduction and in 1 a delay of both auriculoventricular and intraventricular conduction.

An inversion of the T wave in one or more leads was found in 20 cases, in 5 of which it occurred in lead I, in 9 cases in lead I and II, and in 6 cases in lead II and III.

* From the Department of Medicine, University of Minnesota

The average known duration of the existence of hypertension in the cases showing evidence of damage to the heart muscle was approximately five years, as compared with an average known duration of four years in the negative cases

The range of the blood pressure in this group showed 15 patients with a systolic pressure below 200 and 10 with a systolic pressure of 200 or over

Left ventricular preponderance was noted in 44 of the 100 patients in this series (44 per cent), while 56, or 56 per cent, did not show any preponderance. That so great a percentage of the patients should not show left ventricular preponderance was surprising. Various factors were therefore investigated as to their relationship to preponderance. The size of the heart, the ratio between the median right and median left diameters of the heart, the duration of the hypertension, the height of the blood pressure and the condition of the heart muscle, all were studied as to their relation to preponderance.

In the 56 cases which showed negative electrocardiograms, the heart was hypertrophied in 32 cases (57 per cent) and normal in 24 (43 per cent). Of the 32 hypertrophied hearts, 19 were slightly enlarged, 9 moderately enlarged and 4 greatly enlarged. In the 44 cases which showed left ventricular preponderance, the heart was hypertrophied in 32 cases (73 per cent) and normal in 12 (27 per cent). Of the 32 hypertrophied hearts, 11 were slightly enlarged, 16 moderately enlarged and 5 greatly enlarged.

Of the 36 normal sized hearts in the entire group of 100 cases, 12 (33 per cent) showed left ventricular preponderance and 24 (67 per cent) did not. Of the 64 hypertrophied hearts, 32 (50 per cent) showed left ventricular preponderance.

If these 64 cases are grouped according to the extent of the enlargement, it is found that of 30 cases in which slight enlargement occurred, 19 (63 per cent) did not show preponderance and 11 (37 per cent) did. Of the 25 cases which showed a moderate enlargement of the heart, 9 (36 per cent) did not show preponderance and 16 (64 per cent) did. Of the 9 cases with marked enlargement of the heart, left ventricular preponderance was present in 5 cases (55 per cent) and absent in 4 (45 per cent). Although left ventricular preponderance was present in only 50 per cent of the cases with enlarged hearts, these figures show that the frequency of preponderance tends to increase as the enlargement of the heart increases to a moderate degree, and then tends to decrease as the heart becomes markedly enlarged.

The ratio between the median right diameter and the median left diameter of the heart was studied as to its bearing on left ventricular preponderance. Although the ratio between these diameters does not give a true comparison between the relative size of the right and the

left side of the heart, yet the relative value of the ratio was considered to be approximately indicative of the corresponding enlargement of the right and the left side. The results are shown in tables 1 and 2.

If the M R / M L ratio can be taken as an index of the comparative ratio between the size of the right and the left side of the heart, these results would tend to show that there is not a definite relationship between the comparative enlargement of the right and of the left side of the heart and left ventricular preponderance, although here again the tendency to preponderance is greater in the group showing a M R / M L ratio under 50 per cent.

The duration of the existence of hypertension was noted as to its effect on preponderance. It was difficult to obtain correct estimates of the duration of the hypertension as many of the patients had not

TABLE 1—Group Which Showed Negative Electrocardiograms (56 Cases)

	Total No	M R / M L Ratio Under 50%			M R / M L Ratio Over 50%		
		No	Per Cent	Average Ratio	No	Per Cent	Average Ratio
Normal sized hearts	24	12	50	43%	12	50	61%
Enlarged hearts	32	15	47	41%	17	53	60%

TABLE 2—Group Which Showed Left Ventricular Preponderance (44 Cases)

Normal sized hearts	12	7	58%	43%	5	42%	56%
Enlarged hearts	32	25	78%	38%	7	22%	57%

known of the presence of hypertension or had received no medical attention before coming to the clinic. Of those who did know of the presence of hypertension, the duration since first discovered by medical examination was taken as the known duration. It is more than likely that most of these patients had hypertension long before it was discovered by medical examination.

The average duration of the existence of hypertension in the group of patients who did not show any preponderance was 4.55 years in those with hypertrophied hearts and 5.45 years in those with normal hearts.

In the group showing left ventricular preponderance, the duration was 4.8 years in the patients with normal sized hearts and 4.5 years in the patients with enlarged hearts.

Comparatively, the two groups do not show any difference in the time element with respect to preponderance.

That a definite relationship does not exist between the height of the blood pressure, size of the heart and left ventricular preponderance

is shown in table 3. There is little difference in the range of the blood pressure in the various conditions noted. In the cases in which there was left ventricular preponderance, 11 patients (25 per cent) had a systolic blood pressure of 200 or over, and 33 (75 per cent) a systolic pressure under 200. In the group not showing a preponderance, 31 (55 per cent) had a systolic blood pressure of 200 or over and 25 (45 per cent) a systolic pressure under 200. Thus it will be seen that blood pressure alone is not a factor in the production of left ventricular preponderance, in fact, the higher the blood pressure, the less the likelihood of preponderance. A left ventricular preponderance was found in only 11 of 42 cases with a systolic pressure of 200 or over.

When one notes the combined effect of hypertension plus an enlarged heart, it is found that in the group of patients with normal sized hearts, only 1 patient with a systolic pressure over 200 showed left ventricular preponderance, while 10 with a systolic pressure below 200 (between 150 and 200) showed left ventricular preponderance. In the group with enlarged hearts, the effect of enlargement plus hypertension in the production of left ventricular preponderance is noted only when the enlargement increases to a moderate degree. Then only 15 preponderance is present in almost an equal number of instances in patients with a systolic pressure of 200 or over as in those with a systolic pressure between 150 and 200 (9 cases below 200 and 7 cases over 200). When the enlargement becomes marked, there is again a lessened tendency to preponderance with a systolic pressure over 200.

The diastolic pressure has been considered by many observers as indicative of the condition of the myocardium, a relatively high diastolic pressure indicating a poor myocardium and vice versa.

The relationship between diastolic pressure and left ventricular preponderance was observed in this series. A diastolic pressure of 90 was taken as the dividing line. In the group of patients showing left ventricular preponderance, 28 (64 per cent) had a diastolic pressure over 90 and 16 (36 per cent) had a diastolic pressure of 90 or under. In the group which did not show preponderance, 32 patients (57 per cent) had a diastolic pressure over 90 and 24 (43 per cent) a diastolic pressure of 90 or under. It will be seen, therefore, that there is practically no difference in the diastolic pressure in the two groups.

The condition of the myocardium was again investigated with respect to preponderance by means of the other electrocardiographic changes noted. It is known that delayed conduction intervals and negative T waves indicate myocardial degeneration and coronary disease. Whether these pathologic changes in the heart muscle would affect the electrocardiogram with respect to preponderance was noted. Twenty-five cases showed electrocardiographic evidence of myocardial damage. Left

ventricular preponderance was found in 13 (52 per cent) of these cases and in 12 (48 per cent) it was absent. It can be stated, therefore, that the condition of the myocardium as shown by the electrocardiogram does not have any effect on the production of left ventricular preponderance.

COMMENT

From the observations noted, it will be seen that the electrocardiogram does not give any definite information as to the effect of hypertension on the functional efficiency of the myocardium until a true myocardial degeneration has taken place. Then, of course, the electrocardiogram will show evidence of heart muscle disease which

TABLE 3—*Blood Pressure Range, According to Size of Heart and Presence or Absence of Left Ventricular Preponderance in the Electrocardiogram*

Systolic Blood Pressure	150	160	170	180	190	200	210	220	230	240	250	260	Total Cases
Normal sized hearts without left ventricular preponderance	2	2	6	1	2	4	4	2	1	0	0	0	24
Normal sized hearts with left ventricular preponderance	3	0	4	2	2	0	0	0	0	1	0	0	12
Enlarged hearts, 1st degree without left ventricular preponderance	1	1	2	1	2	3	2	1	2	0	0	1	19
Enlarged hearts, 1st degree with left ventricular preponderance	1	2	1	5	0	1	0	1	0	0	0	0	11
Enlarged hearts, 2nd degree without left ventricular preponderance	0	0	0	0	2	2	1	2	1	0	0	1	9
Enlarged hearts, 2nd degree with left ventricular preponderance	0	2	1	1	5	1	0	2	0	3	0	1	16
Enlarged hearts, 3rd degree without left ventricular preponderance	0	0	0	0	0	0	0	2	1	1	0	0	4
Enlarged hearts, 3rd degree with left ventricular preponderance	0	1	0	1	2	0	0	0	0	1	0	0	5

cannot be detected in any other way. How soon these signs will appear cannot be determined by the height of the blood pressure, the enlargement of the heart or the character of the electrocardiogram. In 37 per cent of the cases in this series, the electrocardiogram was negative, among these were cases in which the heart was normal sized and those in which it was markedly enlarged, cases with mild hypertension and with extreme hypertension. There was practically no difference in the duration of the hypertension in the electrocardiographically negative hearts and in the positive ones.

There were fewer cases in which there was a systolic blood pressure over 200 in the electrocardiographically positive hearts than in the negative ones.

The question of left ventricular preponderance brings forth some interesting deductions. When Einthoven first began to use the electrocardiogram in the study of heart disease, he noticed that hypertrophy

of one or the other ventricle produced characteristic electrocardiographic signs. Lewis,¹ however, noted that these changes were not invariably found. He sought the explanation of these difficulties in a study of the relative weight of the two ventricles under various circumstances. He devised a method of sectioning the heart by which the weight of the muscle of each ventricle could be determined separately. The ratio of the weight of the left ventricle to the weight of the right ventricle (L/R) was then determined. He found that this ratio varied greatly and the occurrence of signs of preponderance in the electrocardiogram were attributed to this variance. Hermann and Wilson,² following Lewis' method, except for some minor alterations in the technique, studied a series of fifty-nine cases with regard to the effect of hypertrophy on preponderance. They concluded that the relative weight of the two ventricles is only one of many factors which influence the form of the ventricular complex of the electrocardiogram and that its influence predominates only when the heart is greatly hypertrophied. Cohen³ showed by a series of experiments that the position of the heart in the chest has a far reaching effect on the form of the electrocardiogram. He expressed the belief that the combined influence of the position of the heart and the type of hypertrophy influence the form of the electrocardiogram.

It is known that lesions in the main branches of the bundle of His produce curves similar to those of preponderance. Wilson and Hermann have also shown that lesions which delay the passage of the impulse through one of the bundle branches may produce curves which closely resemble preponderance curves. They do not believe that all preponderance curves are produced in this way. They suggested that possibly variations in the arrangement of the conducting system may have something to do with the form of the electrocardiogram. Both ventricles do not receive the impulse at the same time, and it is probable that in preponderance curves the precedence of one ventricle over the other may be unusually great.

The clinical study of these various factors in this series of cases tends to show that while hypertrophy of the left ventricle and a relative disturbance of the L/R ratio are factors in the production of left ventricular preponderance, they are not determining factors, as 38 per cent of the hearts which showed preponderance were not enlarged and 57 per cent which did not show preponderance were enlarged. That

1 Lewis, T. Observations upon Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber, *Heart* 5 367, 1913-1914.

2 Hermann, G. R., and Wilson, F. N. Ventricular Hypertrophy. A Comparison of Electrocardiographic and Postmortem Observations, *Heart* 9 147 (April) 1922.

3 Cohen, Alfred E. An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9 311 (Dec.) 1922.

the hypertension was not a factor is shown by the study of the blood pressure range in the various groups of this series. Only 44 per cent of the cases showed preponderance. That hypertension may have a deterrent effect in the production of preponderance is shown by the fact that, in the group with normal sized hearts, only one case with a systolic blood pressure over 200 showed left ventricular preponderance, while ten cases with a systolic pressure between 150 and 200 showed preponderance.



Chart 1—Electrocardiogram of a patient taken Jan 23, 1924, showing left ventricular preponderance

Whether delayed conduction had any bearing on the curve of preponderance cannot be stated, although none of the cases with delayed conduction showed left ventricular preponderance. Of all the cases with evidence of myocardial damage as shown by delayed conduction and negative T waves only 52 per cent showed preponderance.

That there are other factors involved in the production of left ventricular preponderance may be assumed from the following instances. In charts 1, 2 and 3 the tracings taken at different intervals show first left ventricular preponderance, then no preponderance and finally prepon-

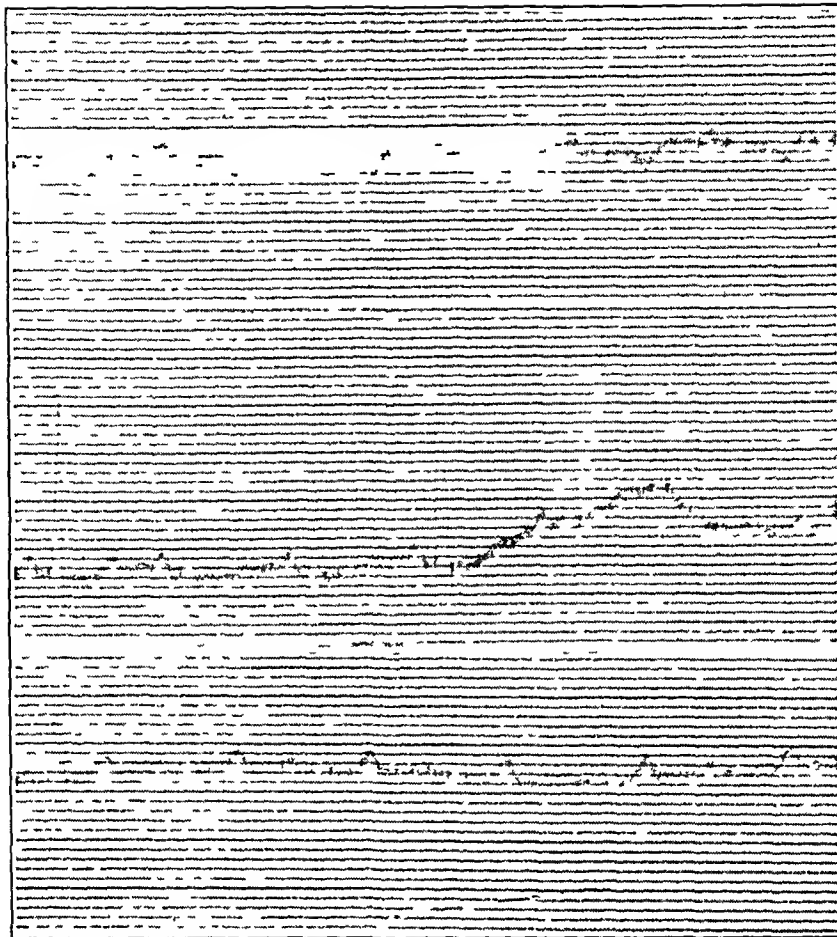


Chart 2—Electrocardiogram of same patient taken Oct 29, 1926, showing no left ventricular preponderance

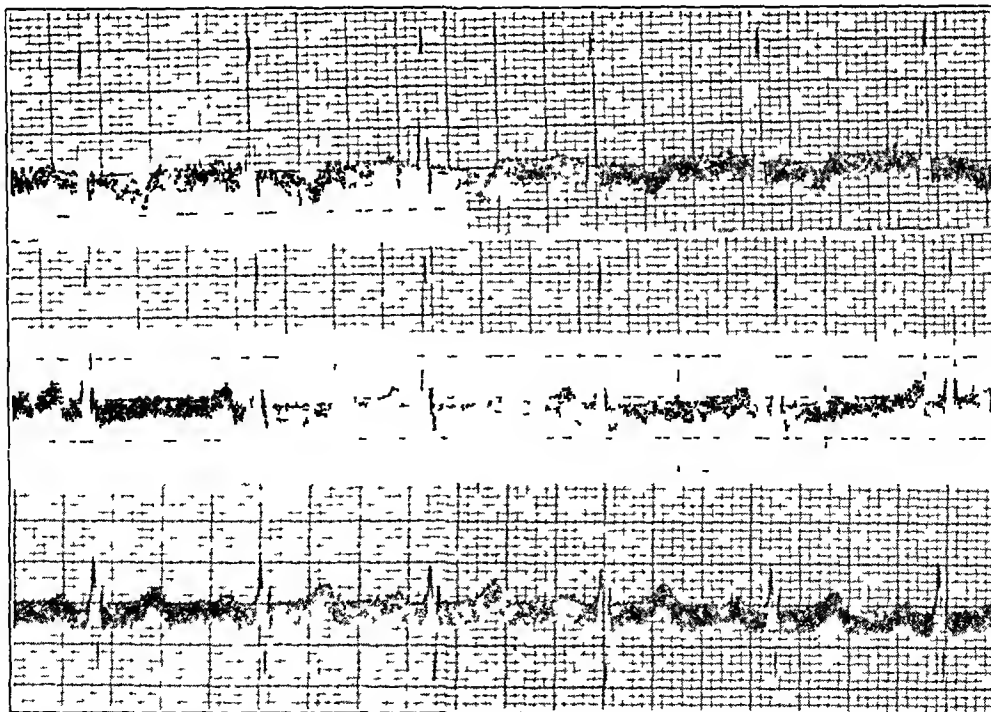


Chart 3—Electrocardiogram of same patient taken April 6, 1927, again showing left ventricular preponderance

derance again. During the period involved, the size of the heart has remained practically the same as shown by the roentgen-ray examinations. The blood pressure has remained constant and the clinical symptoms have not changed.

It has been shown that left ventricular preponderance of the heart in myxedema disappears after thyroid medication.

SUMMARY AND CONCLUSIONS

1 The electrocardiogram per se does not give any definite information as to the effect of hypertension on the heart until a myocardial degeneration has taken place.

2 The interval after which this occurs cannot be determined clinically.

3 Left ventricular preponderance is not always present in hypertensive heart disease. It was noted in only 44 per cent of this series.

4 Left ventricular hypertrophy, while a factor in causing left ventricular preponderance, is not a determining factor.

5 The frequency of left ventricular preponderance tends to increase as the enlargement of the heart increases to a moderate degree, and then tends to decrease when the heart becomes markedly enlarged.

6 There is no definite relationship between the comparative enlargement of the right and left side of the heart, as indicated by MR/ML ratio and left ventricular preponderance. The tendency to left ventricular preponderance is greater, however, in the group showing a MR/ML ratio under 50 per cent.

7 The duration of the existence of hypertension does not have a bearing on left ventricular preponderance.

8 Hypertension alone does not produce preponderance. In fact, the tendency is the other way, the higher the blood pressure, the less likelihood of left ventricular preponderance.

9 The condition of the myocardium as shown by other electrocardiographic changes does not influence the production of left ventricular preponderance.

10 Other factors, besides those enumerated, and at present unknown, are involved in the production of left ventricular preponderance.

ULCERATION OF THE ESOPHAGUS

EXPERIMENTAL STUDY [†]

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AND

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In the course of our clinical study of ulceration of the esophagus, it was evident that, up to the present, insufficient attention has been directed to this disease, which according to our experience is more common than has ordinarily been reported in the literature. On this account, an attempt was made to determine experimentally certain important diagnostic problems associated with this condition.

In our experiments, nineteen dogs were utilized. The dog is a favorable subject for experimental study of this disease, as ulcerations can be produced with but slight difficulty following which x-ray and esophagosopic examinations can be readily performed.

The following types of ulcerations were produced: (1) mucosal lesions, (2) penetrating ulcers, (3) perforating ulcers.

METHOD OF PRODUCTION OF ULCERS

As our study of ulcerations of the esophagus was undertaken primarily with the object in view to clear up certain questions in diagnosis, it made but slight difference as to the method of the formation of the ulcer. On this account, traumatic ulcers were produced by means of a biting instrument passed through the esophagoscope. At first, mucosal erosions were produced by scarification of the mucous membrane, but as these ulcers healed too rapidly, they were unsatisfactory for study. Even following a single application of phenol or lye on the small eroded area, healing occurred so rapidly that signs of the lesion did not remain after a week. It was then decided to produce deep penetrating ulcers which would probably remain unhealed for a longer period and would therefore be more adaptable for this study. These were produced by removing deep portions of tissue. These ulcerations also had a tendency to heal rapidly, though they would remain unhealed for a longer period than the superficial mucosal erosions.

* From the Gastro-Enterological Clinic of the Department of Medicine and the Pharmacological Laboratory of the University of Maryland.

* Read at the meeting of the Association of American Physicians in Washington, May 3, 1928.

In an attempt to produce chronic ulcers simulating chronic peptic ulcerations of the esophagus, we administered large quantities of a 10 per cent solution of hydrochloric acid through a tube following the production of these lesions. Two drachms (7.5 cc) of the acid was administered four times daily for varying periods extending over several days to several months. Interesting results were obtained in this study, as the mucosal ulcers as well as the penetrating ulcers were transformed into chronic ulcerations by this procedure. Lye was utilized in several instances for this purpose, but with less satisfactory results, as the lye would occasion numerous erosions throughout the esophagus while the hydrochloric acid would not affect the normal esophagus but only the area in which the ulcer was situated.

As a result of these experiments, it was demonstrated that active ulceration could be maintained over long periods. In six normal control dogs in which hydrochloric acid was similarly administered, ulceration could not be detected, though occasionally small erosions were observed which were due to the trauma produced by the insertion of the esophagoscope or stomach tube. When large doses of acid were frequently introduced through a tube into the esophagus of a dog, considerable bleeding of the ulcer was observed through the esophagoscope. This bleeding usually occurs as soon as the ulcer has formed and in most instances continues as long as the acid is administered. If the administration of acid is continued over a varying period of time, the animal will usually begin to regurgitate large quantities of blood mixed with mucus. One also observes that the animal loses much weight during this period, notwithstanding the fact that he still continues to consume the usual quantity of food and that he becomes anemic. If the ulcers were allowed to heal and acid was not administered during the intervening period, the further application of acid did not disturb the scar or produce any effect on the esophageal wall.

In the erosion or mucosal type of ulcer, feeding with acid prevents rapid healing, but in the penetrating ulcers the continuous use of acid will frequently produce perforation or healing is markedly retarded. In seven dogs, the mucosa of the esophagus was scarified. In three of these, acid was not administered, these ulcers healed promptly, while in four in which acid was given bleeding ulcers were produced in which healing was greatly delayed. Even in the animals with deep ulcerations healing was prompt when the animal was not treated with acid, while when acid was given perforation was frequently produced. In every instance in which the acid was administered, regardless of whether the ulcer was superficial or deep, the ulcerated area was usually increased in size to an extent dependent on the length of time of the treatment. Lye was administered to two dogs over a period

of two months. Large doses (a half teaspoonful to one teaspoonful of concentrated powder dissolved in 3 ounces [89 cc] of water) were given twice daily over a period of four weeks. Numerous ulcers were noted during the esophagoscopic examinations, which were performed weekly. These ulcers appeared superficial and bled easily and

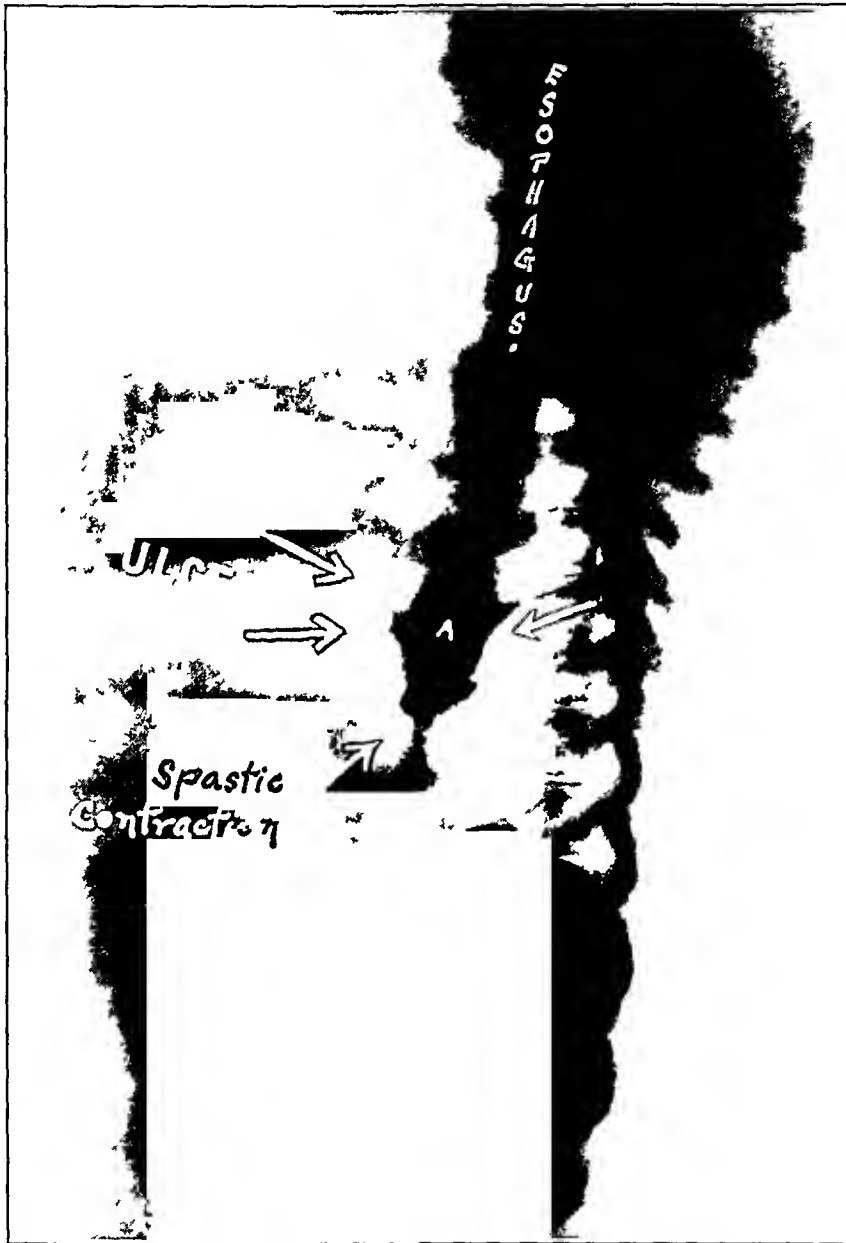


Fig 1 (dog 13) —A large ulcer crater filled with barium overshadowed by the surrounding esophagus, confirmed by esophagoscopic examination, cardiac end shows typical spastic contraction frequently noted in ulcerations

freely. However, following discontinuance of the use of the lye, healing occurred promptly, and on further examinations the esophagus was found to have assumed a normal appearance in a single instance, while in the others, numerous small pinkish areas were observed which

indicated that the ulcers had almost completely healed. This was verified at autopsy. Bleeding was a persistent and constant sign in all of the active ulcers, though serious hemorrhages were not encountered in this series. Strictures followed by obstruction were not noted. A marked increased secretion of mucus was also observed. It is of great advantage to have roentgen-ray investigations precede esophagoscopy, as has also been recognized in human beings.

Due to the difficulty encountered in visualizing the esophagus when obstruction does not exist, it is necessary to administer the opaque barium meal in a continuous flow in order to obtain satisfactory roentgenograms. The animal is placed on the abdomen with a special gag in the mouth, and through an opening in the gag the stomach tube is passed

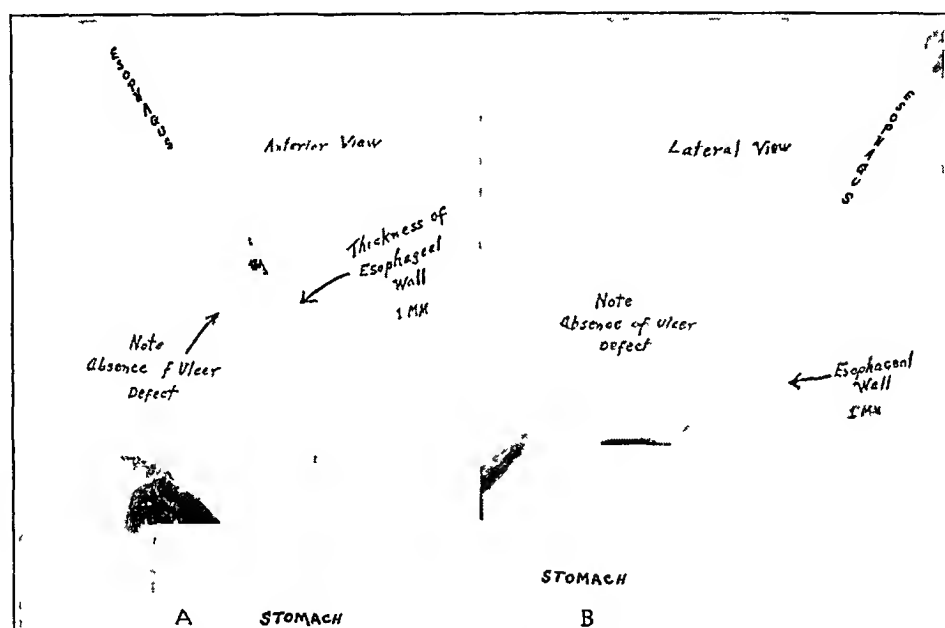


Fig 2 (dog 13) —A, specimen obtained at autopsy. Anterior view. Ulcer allowed to heal. The absence of the filling defect should be noted. The condition was confirmed by esophagoscopy and at autopsy. B, lateral view.

into the esophagus for about 6 inches (15 cm) from the teeth. After one is certain that the tube is in the esophagus, it is then attached to another tube which is connected to the barium container, the barium meal is allowed to flow into the esophagus slowly but steadily by means of gravity. During the x-ray examination films are taken in two positions, oblique and postero-anterior. The flow of barium is discontinued, and another film is taken in the oblique position when the esophagus has emptied itself. This is an important procedure.

Experimental ulcers of the esophagus produce essentially three types of filling defects: (1) defects projecting from the esophageal outline, (2) defects partly displacing the esophageal outline, and (3) spastic defects.

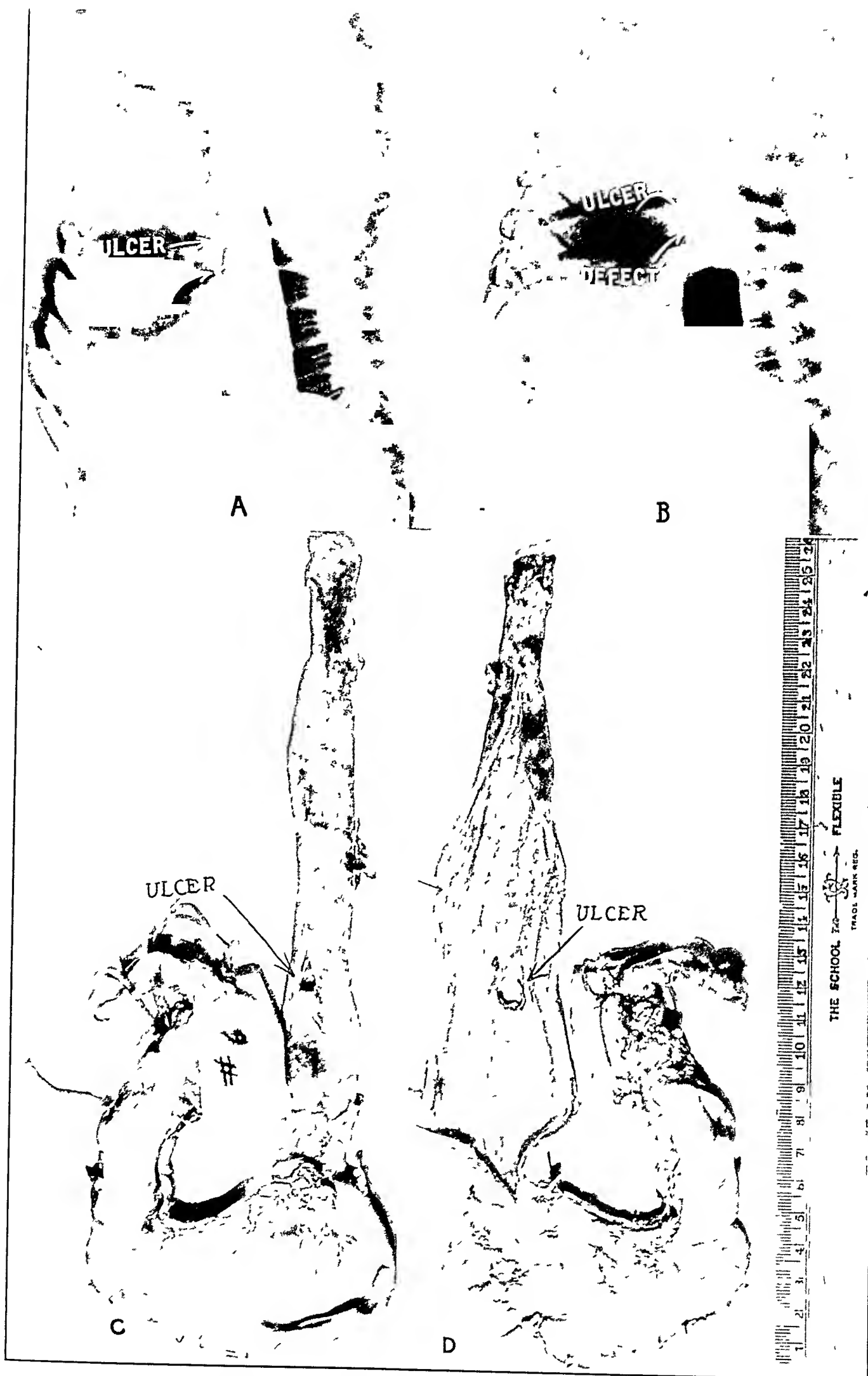


Fig 3 (dog 6) —A, esophagus when filled showed a displacing type of filling defect. This was confirmed by esophagoscopy examination. B, the typical ulcer defect of the penetrating type when the esophagus is empty should be noted. C, perforation following the administration of 10 per cent hydrochloric acid solution. D, shows the size of the perforated ulcer, with the esophagus opened.

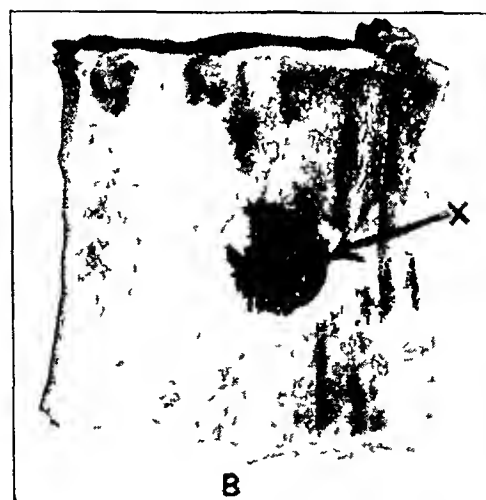
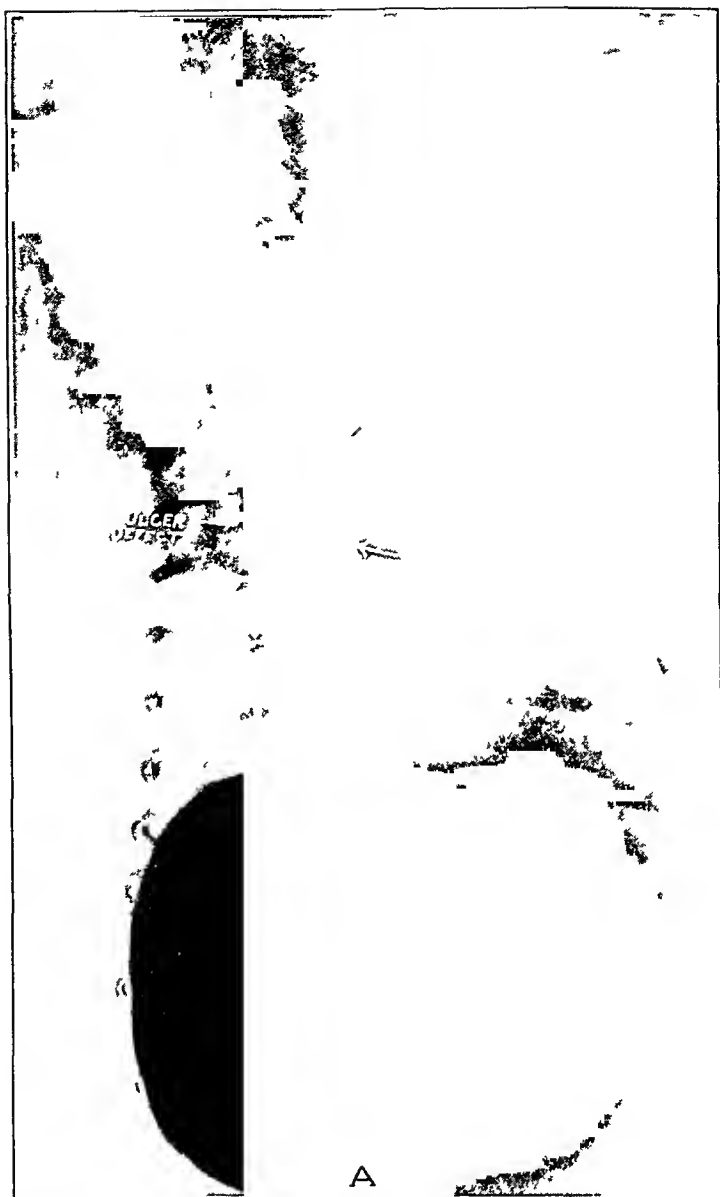


Fig 4 (dog 12) —*A*, small penetrating ulcer defect on the right posterolateral wall, with slight displacing defect opposite. This was confirmed by esophagoscopic examination. *B*, the dog was killed five days following the administration of 2 drachms of 10 per cent hydrochloric acid solution four times daily. The large punched out ulcer crater should be noted. *X* indicates the ulcer.

The diagnosis of ulcer of the esophagus is made roentgenologically in a manner similar to that observed in gastric ulcer. A persistent filling defect is direct evidence of this condition. However, defects are frequently extremely difficult to demonstrate when present in the esophagus largely due to the location of the ulcer and the position in which



Fig 5—The tapering spasm frequently found in ulcer of the esophagus

the x-ray examinations are made. Filling defects are frequently best observed immediately following the emptying of the esophagus of an opaque meal. The ulcer crater will under these conditions retain sufficient of the barium meal to reveal a shadow varying in extent according to the size of the ulcer. On the other hand, the ulcer will at times

show to best advantage when the esophagus is well filled. This is especially true in those instances in which deep penetrating and perforating ulcers exist.

Mucosal ulcers do not always reveal defects in the roentgen-ray examinations, as the crater is often too shallow, but may in some instances show a small fleck situated in the ulcerated area after the esophagus has emptied. These ulcers, however, frequently present a spasticity which is often characteristic of this type.



Fig 6—*A*, large penetrating ulcer on lateral wall at *U*. *S* shows marked spasticity with signs of obstruction. *B*, same dog, showing perforation.

Penetrating ulcers, when large, frequently simulate diverticula. The defect produced by this form of ulcer is of the projecting type, which is typical and characteristic of this lesion. It is observed as a large regular or irregular shadow when the esophagus is empty, or as a defect or niche when it is filled. Occasionally, a defect will not be observed at first, but if the examination is repeated, it may show subsequently in another position.

On account of the thinness of the wall of the esophagus in dogs, perforation not uncommonly follows as a complication in ulcerations.

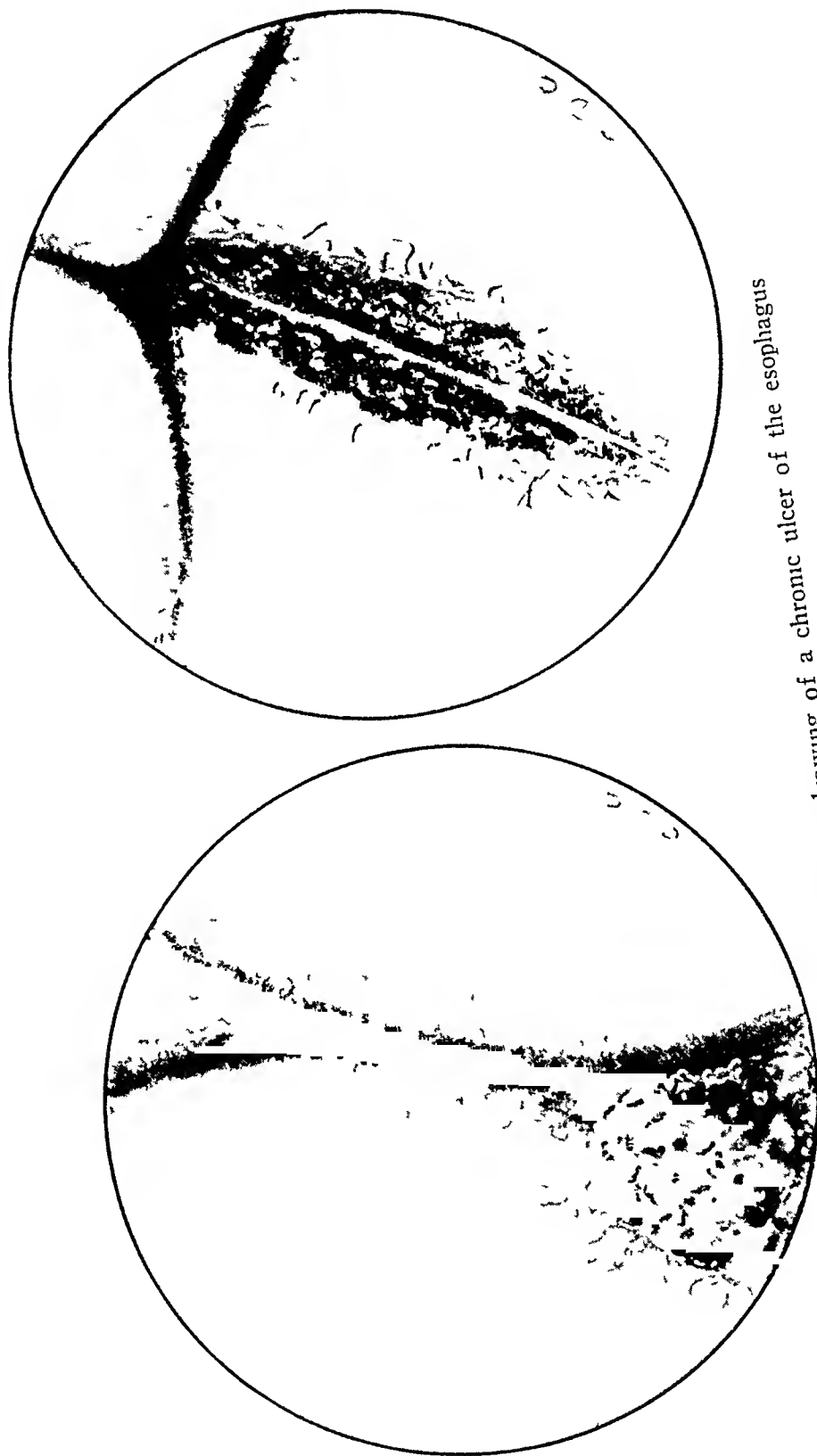


Fig 7—Esophagoscopic drawing of a chronic ulcer of the esophagus

The perforating ulcer is also revealed roentgenologically as a projecting type of defect. Spasm of the esophagus is frequent, the characteristic spasm caused by an ulcer is of the tapering type, but at times spasm may be observed which produces a displacing defect opposite the ulcer or in the ulcerated area. Occasionally, spasm may be so marked as completely to cut off the barium meal, giving the appearance in the picture of an organic obstruction. By means of esophagoscopic examinations, these ulcerations were observed directly and their size noted and bleeding detected, a grayish membrane and pinkish white scar were revealed when healing occurred. In the ulcer that has been present a

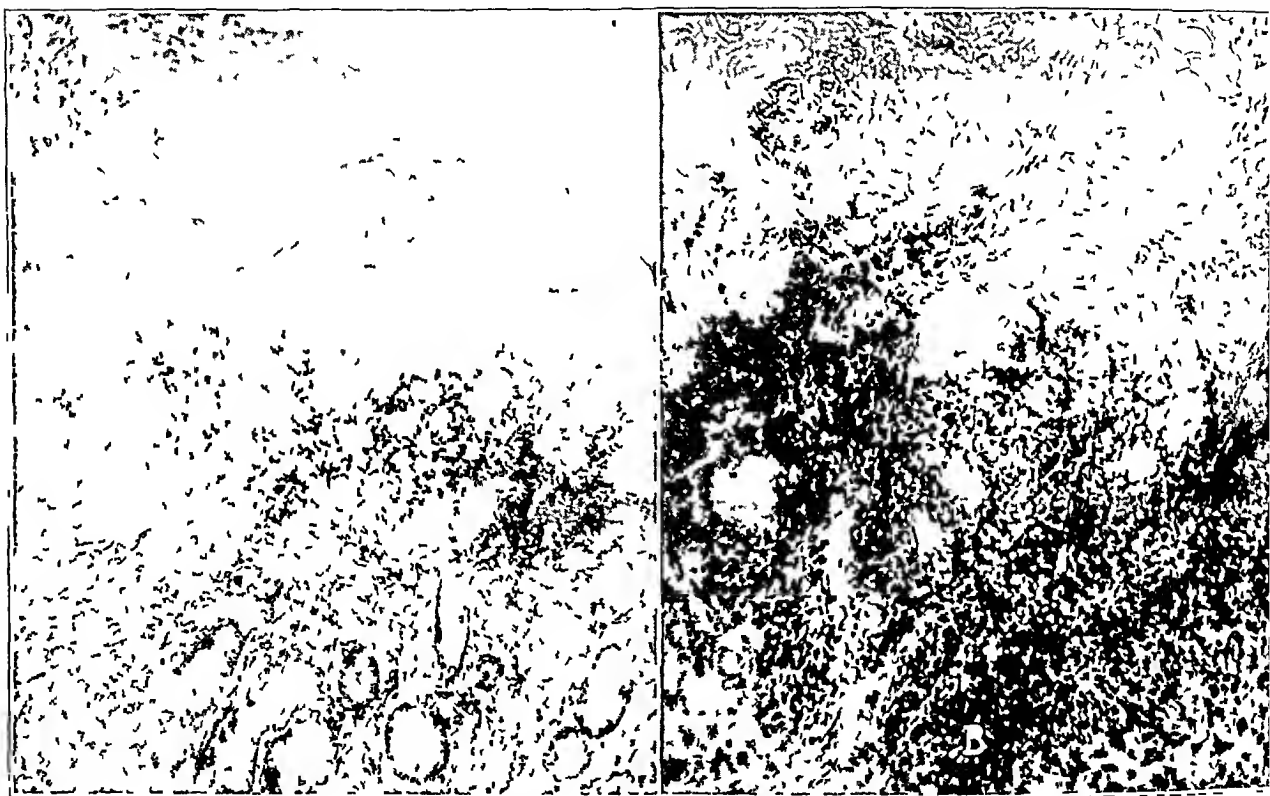


Fig 8—*A*, an ulcer undergoing extensive necrosis. Low power magnification. *B*, high power magnification of *A*.

long time, definite induration and thickening were not noted. The ulcer appears well defined, and its edges are sharply outlined and are occasionally everted and irregular. The base of the ulcer appears smooth and is apparently regular. These observations were confirmed by the condition found at autopsy. The ulcers bleed readily when touched with an applicator during the esophagoscopic examination. Fixation of the esophagus, as is occasionally found in the human being, was not noted in these experiments. The esophagoscopic appearance closely resembles ulcers of the peptic type. In this form of ulcer, it is dangerous to remove specimens for pathologic study for fear of producing perforation.

It is interesting to note that diet plays but a slight rôle in the healing of these ulcerations. Even when the animals were fed with bones and tough meat, a change in the appearance of the ulcer could not be detected. When these ulcerations are fully established, the animal exhibits difficulty in swallowing with evidence of pain when food passes over the ulcerated area.

The pathologic appearance of a typical ulcer, as was observed in dog 12, is characteristic. The gross specimen shows a large round ulcer in the lower third of the esophagus on the lateral and posterior aspect, about 8.5 cm from the cardiac orifice and measuring 12 by 15 mm and about 2 mm in depth, the floor of the ulcer is relatively smooth, with a slight sloping toward the center. The edges are clean-cut and slightly everted. The mucosa near the ulcer appears normal. The

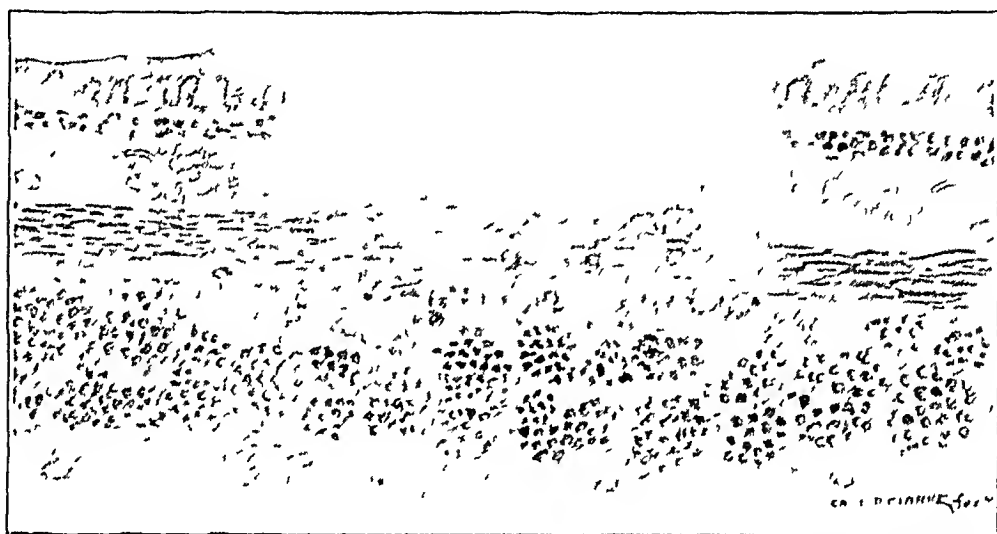


Fig 9—Microscopic drawing of a typical ulcer of the esophagus

ulcer has the appearance of a peptic ulcer such as is observed in the stomach and duodenum.

Sections of the esophagus present the ulcer extending into the inner circular muscular layer and in its deeper portion involving the adjacent muscle bundles. Toward the edges, the ulcer does not extend any deeper than the submucous layer. The floor of the ulcer is covered with fibrin and pink staining necrotic tissue. Throughout this area and in the adjacent living tissue, there is a moderate diffuse leukocytic infiltration. The outer fibrous coat and the muscular coats are edematous and show a moderate leukocytic infiltration. The blood vessels at the base of the ulcer are dilated and contain red blood corpuscles. Leukocytic margination is observed. Similar though less marked vascular changes are noted in the more remote tissues. A number of the smaller arteries and capillaries in the tissue beneath the floor of the ulcer contain

hyaline thrombi. The stratified squamous epithelium (mucosa) ends abruptly at the edge of the ulcer, beyond this point on either side, it appears normal. The submucous glands beyond the area of ulceration are normal.

CONCLUSIONS

1. Ulcers of the esophagus produced by removal of a small section of the wall through the esophagoscope will heal readily within a week.

2. Ulcers when treated with a 10 per cent solution of hydrochloric acid will become chronic, and healing will be markedly retarded.

3. Perforation is a frequent occurrence when deep penetrating ulcers are treated with acid.

4. Ulcers when uncomplicated do not form strictures but heal readily.

5. The x-ray examination reveals defects and spasm in most instances, which are characteristic of ulceration.

6. Large penetrating ulcers may simulate diverticula.

7. The ulcer is clearly demonstrated on esophagosopic examination.

PALM COLOR TEST

A SIMPLE, PRACTICAL CLINICAL METHOD FOR THE DIAGNOSIS OF
ANEMIA AND PLETHORA

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KANSAS CITY, MO

I shall describe in this paper a simple, practical clinical test which is useful in the diagnosis of anemia and plethoria, and which is accurate and dependable in the hands of those who are well acquainted with it. In fact, I believe, it is one of the most accurate and dependable methods of detecting slight grades of anemia or plethoria. Through its use, one can detect a gain or loss of 200 cc of blood given by transfusion or withdrawn by venous section.

In the earlier days of medical science, a diagnosis of anemia or plethora depended on examination of a patient's color, or the color of a freshly drawn specimen of blood. In more recent years, laboratory estimations of the red count and percentage of hemoglobin have gained precedence over this simple practical method of examination. Since the introduction of methods of estimating plasma volume and blood volume, there have been additional valuable means of making more accurate the laboratory diagnosis of anemia and plethoria. With many physicians, the use of one or several laboratory methods has completely supplanted the common sense observation of a patient's color. This is unfortunate, for laboratory examinations, per se, occasionally lead to gross and often unfortunate error in judgment, both in diagnosis and treatment. Furthermore, laboratory methods are rather complex and are not at the disposal of the profession at large. Finally, laboratory tests are not always at the disposal of the relatively few who are sufficiently practiced to make them and interpret the results correctly.

The commonly used blood counts and hemoglobin estimations do not tell the whole story concerning the presence or absence of anemia or plethoria because of the fact that an important factor still remains unknown, namely, blood volume. It is a well known fact that a patient with a normal red count and percentage of hemoglobin may be anemic or plethoric because of an abnormal blood volume. At the present time, there is available to the profession an ingenious method of estimating plasma volume and blood volume. Results of this combined with red counts and hemoglobin estimations might deceive one into believing that these results can be used infallibly in the diagnosis of anemia and plethora. This happy state of affairs does not exist at the present time, for even with these results obtained with flawless technic, there is still an important

unknown quantity which prevents their use without limitation in diagnosis, one remains at a loss to know whether or not the results actually found are the optimum for the patient under observation, or whether they are too high or too low. One is confronted with the same obstacle that is presented in basal metabolic estimations if it is impossible for some reason to calculate theoretically the normal rate of oxygen consumption for the patient under observation and for this reason one is unable to decide whether the results actually found in the patient are normal or abnormal.

There are at the present time relatively accurate methods for estimating blood volume for given persons. There is no infallible method, however, for calculating theoretically what the blood volume for the person ought to be and, therefore, one may be at a loss to know whether or not the result found is the optimum for the patient. This state of affairs should seem self-evident to those who will bear in mind that some persons are muscular and active and naturally demand a greater blood volume per unit of weight than fat phlegmatic persons with small muscles and small internal organs. A volume of blood which would be normal for an athlete such as a professional wrestler would naturally be too great for a patient with hypopituitary obesity, who might have the same height and weight. It is self-evident that fatty tissues contain less blood per unit of weight than active muscle tissues and much less than the internal organs such as the spleen, liver, and finally the heart and large blood vessels. Greater difficulties are encountered under certain pathologic conditions in which the capacity of the vascular system is increased or reduced by cardiac or vascular anomalies, aneurysms, malignant conditions, pregnancy, and other conditions, and on this account, the blood volume optimum per unit of weight is made unusually great or small. If one has an accurately determined red count and percentage of hemoglobin, therefore, and an accurately determined blood volume, one still lacks in many cases, the information which is desired most of all, namely—a knowledge as to whether the patient has exactly what he needs in the way of a total quantity of circulating hemoglobin.

These are not the only difficulties to be encountered under pathologic conditions. It was pointed out by Dr. D. D. Stofer and myself¹ a number of years ago, that in one of the most important and most common forms of anemia, namely, pernicious anemia, there is a state of affairs which makes all methods of examination go awry. This state of affairs consists of a marked difference between capillary and venous red counts. I found that the capillary blood count is always much higher than the venous blood count in pernicious anemia, and that in the average case this difference amounts to as much as from 500,000 to 1,000,000 cells or more per cubic millimeter of blood. This difference in the case

¹ Duke, W. W., and Stofer, D. D. A Comparison of Capillary and Venous Blood in Pernicious Anemia, *Arch. Int. Med.* **30**: 94 (July) 1922.

of severe anemia is gross indeed, in fact, it is not uncommon to find a capillary count more than 50 per cent greater than the venous count. Red counts, hemoglobin estimations and blood volume methods used in this disease, therefore, give a false idea concerning the actual status of the volume of circulating hemoglobin.

One may as well admit frankly, therefore, that in studying anemia, variables and obstacles are encountered which, under certain conditions, seem discouragingly gross. This and the foregoing statements are not made for the purpose of throwing discredit on present day laboratory methods, they are made rather for the purpose of pointing out that laboratory methods at best have their shortcomings. They actually



Fig 1—Note a marked difference in color between the two hands of normal persons because of difference in position. A difference as marked as this between the color of a patient's hand and the control would indicate a large difference in the mass of circulating hemoglobin (from 3 to 4 points of normal blood) if the test was made as described in the text. The photograph illustrates how little can be gained by examination of the skin of the face, the lips or the conjunctivae if the posture of the patient is not taken into account. When the patient is in a lying posture the face surfaces are more highly colored than in an erect posture. If the face is below the level of the base of the heart, the degree of redness becomes still more marked.

equal, I believe, or possibly exceed the shortcomings of the color test to be described, which is so simple that it can be used by any physician who has what is commonly known as horse sense.

It is a time honored custom for physicians to diagnose anemia or plethora by observing a patient's color, that is, by observing the color of

the face, lips, conjunctivae or nails That this method of diagnosis is inaccurate should seem self-evident A moment's observation of the faces of one's friends should immediately disclose the fact that of persons who believe they are normal, some have red faces, others pale faces, some red lips, others pale lips, some rosy ears and others pale ones Even the color of the nails and back of the hands varies greatly in normal persons Furthermore, the color of a person at different times in the day will vary grossly in these localities The face, an organ of expression, is subject to marked variation in color under the influence of many factors, such as the emotions, change in external temperature or exercise The color of the skin generally varies greatly with temperature and exercise because of the function of the skin in regulating the loss of body heat A physician, therefore, cannot gain reliable information concerning an abnormality in the blood by observing the color of these parts unless the change is marked indeed The conjunctivae, a time honored location for the observation of color, are also subject to variation under conditions other than those due to change in the total quantity of blood The color changes, for example, if a patient changes from a sitting to a lying posture The importance of this variable factor can be seen in figure 1 in which the color of the hands can be compared, one of which is about 1 foot (30.4 cm) higher than the other² The conjunctivae, with a change from sitting to lying posture, vary owing to the fact that in the erect posture, the vessels of the head tend to be emptied by a column of blood under negative pressure This gives rise to a difference in color which is marked, indeed, and which is never taken into account by clinicians So great a difference in two patients in the same posture might indicate a marked pathologic process When anemia is marked, pallor of the conjunctivae can be observed with definiteness When plethora is marked, a tinging of the sclerae with pink becomes evident and practically always indicates a serious pathologic increase in blood volume unless accounted for by a local pathologic change These changes in the conjunctivae can be observed definitely when caused by gross pathologic changes in the blood,

2 It is extremely difficult to photograph color accurately even under ultraviolet light A slight change in the slant of the hand casts a shadow which appears as darkness and could be interpreted as color In all the illustrations, an effort has been made to photograph the hands satisfactorily and to show their color in the various stages at which blood volume has been increased or reduced by transfusion or venous section, as the case may have been When photographs were taken, red counts and hemoglobin estimations were usually made Unfortunately, in the great majority of cases the color photographed did not give a true picture of the color observed The photographs which are shown are only illustrative figures which approximate the changes in color They do not faithfully record events as they actually occurred, and in many instances red counts and hemoglobin estimations were not adequately made at the time the photographs were taken

but cannot be observed with accuracy nor definiteness when the pathologic change is slight but yet important. The diagnosis of anemia or plethora from the color of the face and conjunctivae are unsatisfactory and inaccurate for another reason, namely, because of the fact that the color is not easily compared with a standard. The color of a patient is usually compared instead with the physician's idea of normal color. Here, personal equation is of necessity a source of gross error. One's own idea of normal color changes from time to time, in fact, to a surprising extent from day to day. This crude method stands in marked contrast with the nicety with which blood volume is regulated by nature in a healthy person. It has properly been nearly supplanted by laboratory examinations, in a struggle for accurate standards.

Hemoglobin estimations of a sample of blood are made at the present time by comparing the color of a patient's blood directly or indirectly with the color of an average specimen of normal blood, that is, by a colorimetric method and by a standard which amounts to nothing more nor less than an average found in normal persons. This method is accepted as fair. The method of testing color to be described is likewise a colorimetric method, but *in vivo* instead of *in vitro*. It depends on a comparison of the patient's color with the color of the average normal person. It would seem on first thought that this could be accomplished by examination of any of the surface tissues. This, however, is not the case for, as previously mentioned, most tissue surfaces vary in color under many conditions other than those caused by anemia or plethora.

There exists one skin surface in which color varies remarkably little unless a person is anemic or plethoric, and from its color an idea can be gained concerning the quantity of hemoglobin which is actually in the general circulation. This surface is the palm of the hand.

The palm of the hand is meant for work. It is not an organ of expression, subject to marked normal variation in color like the face, nor is it a surface designed, I believe, to help to any marked extent in regulating the loss of body heat as is the skin surface generally. Furthermore, it is not often exposed to direct sunlight, so consequently its color is not influenced much through this agency. For these reasons, marked and frequent constriction or dilatation of the vessels of the palm would seem less purposeful physiologically than for vessels of other surfaces of the skin. Practically it is not often marked—at least under conditions under which a patient sees a physician in his office, home or in hospital practice. This statement is based on thousands of observations that I have made during a period exceeding ten years. The color of the palm of the hand is remarkably constant under the usual normal conditions of living. The palm of my own hand compared repeatedly with those of several assistants from time to time is always exactly the same.

METHOD

If a physician's palm is normal in color, it can be compared with the patient's, and slight differences in color can be estimated with accuracy. This is true whether the patient examined is a day laborer with calloused palms, or a woman with thin skin, or a child. It can frequently be made with relative accuracy even in pigmented races, such as the Indians. In many of the pigmented races, the palm of the hand is pigmented less than the skin generally, and often little at all. Furthermore, the estimations can usually be made whether a patient is sick or well, emotionally upset or otherwise. Relatively few physiologic conditions and few illnesses, other than anemia or plethora, change

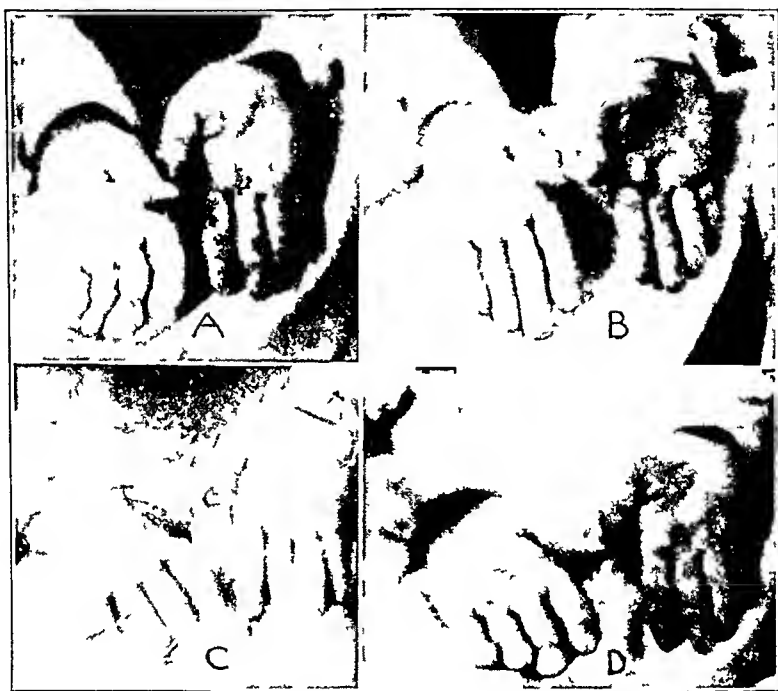


Fig 2—In *A*, the palm on the left is that of a man weighing 220 pounds (99.7 Kg) who had a severe acute hemorrhage from the gastro-intestinal tract. The red count was 2,880,000, the hemoglobin, 50 per cent. The palm of the hand appeared almost bloodless. The illustrations (taken by daylight) reproduce poorly the enormous changes in color which were actually observed. *B* indicates the palm after the introduction of 1,340 cc of blood by direct transfusion from two large plethoric donors, the red cell count was 3,624,000, the hemoglobin, 65 per cent. *C* shows the palm after the introduction of an additional 1,200 cc of blood by direct transfusion from two donors, red count, 4,168,000, hemoglobin, 80 per cent, normal color not completely established, and *D*, after a lapse of two weeks, the red cell count was 4,320,000, the hemoglobin, 80 per cent. Color was not completely re-established in this patient because of the fact that he was plethoric prior to his hemorrhage with a red count of 6,560,000. It was assumed that he would soon re-establish normal color, if not an increased color, without further addition by transfusion. At a later date he was bled because of recurrence of polycythemia.

the color of the palm in marked degree. Several important exceptions will be mentioned subsequently. Additional exceptions may be discovered in the course of time.

The technic of comparing a physician's palm with that of a patient would seem simple. The fact is, however, that it is not simple, and unless the comparison is made accurately and in a definite way, it will prove grossly misleading.

In the first place, one must know whether or not the physician's palm is normal. This can be determined by comparing the physician's palm with that of many young healthy adults. If the physician's palm proves normal in color it can be used as a standard for comparison with patients. Otherwise, it cannot be used, and some other person must be chosen for a standard.

When the comparison is made, both patient and physician should either stand or sit comfortably. The hand of each should be semiflexed and should be held at about the level of the apex of the heart, or a little above for a few moments, until constant permanent color has been established. It is essential that the distance between the hand and the base of the heart be identical in both physician and patient, and that in neither should the skin of the palm be stretched. One can convince himself of the importance of these two statements if he will compare his own palms, one hand semiflexed and the other markedly extended, and if he will raise one hand above the level of the other for a moment and then compare the color of the two. This makes a gross difference almost immediately. Interesting red and white spots, should they appear, can be eliminated if both the hand of the patient and standard are held at a slightly higher level.

If these details are attended to, the color of the patient's palm can be compared with the physician's standard. Under the usual normal conditions, the color of both patient and physician will be practically identical as to both fingertips and palm. If the patient is slightly anemic, his plan will be paler than the physician's, the fingertips may appear the same. If the patient is anemic (secondary anemia) to such an extent that the red count or percentage of hemoglobin is definitely reduced, the difference in color between the patient's hand and the physician's will be so striking that it could not possibly be overlooked. The patient's fingertips and palms will both look pale, by comparison. If anemia is of such a grade that the red count lies much below four million, the patient's palm will look almost bloodless as compared with the physician's (exceptions to be mentioned subsequently). If the patient is plethoric, the change is equally striking. If he is plethoric to such an extent that the blood count or percentage of hemoglobin is definitely increased, the abnormal redness will be so marked that it could not possibly be overlooked.

With practice in the use of this method, a physician can become so expert that by making this comparison in color, and noting the size and muscular development of a patient, he can predict with relatively small error the quantity of blood which will be required by transfusion to re-establish normal color in an anemic person. He can likewise, though with less accuracy, predict in plethoric persons the quantity of blood which will have to be removed by venous section to establish normal color. He can, furthermore, tell with relative accuracy when an optimum quantity of blood has been given during transfusion, and when the transfusion should be stopped. These statements are based on a broad clinical experience in which the test has been used thousands of times and compared with clinical and laboratory observations and with the results of transfusion in anemic patients and venous section in plethoric patients. It has been used as a guide during more than 1,000 direct transfusions of blood and has proved dependable and useful.

EXCEPTIONS TO THE RULE

Relatively few common conditions other than anemia or plethoria change the color of the palm in a person indoors and at rest. Red and white spots, if present, may interfere with the accuracy of the test, this difficulty can be overcome by elevating the hands a little. Cyanosis, or jaundice, if marked, may seriously interfere. Patients with Renaud's and other diseases of the arteries or veins, with chilblains, and patients whose hands have been scalded, or kept in hot water a great deal, usually have abnormal palms as the result of local conditions in the extremities, and in these the test cannot be made with accuracy. Furthermore, in patients with certain diseases of the skin, in patients in syncope or shock and in a few patients with goiter, the test is not accurate. Furthermore, I have gained the impression that the Latin races and persons living in hot climates under normal conditions tend to have more highly colored palms than the average person in this district. Furthermore, rather obese persons who are over middle age often show more color than usual. This may be pathologic, or may be a compensation to increase surface cooling in the obese, on the other hand, it may indicate a mildly pathologic condition which needs correction in the same sense that obesity indicates the desirability of correction. Finally, in some forms of anemia, namely, pernicious anemia, one encounters the unusual factor which has been mentioned, namely, a tendency for the corpuscles, especially the macrocytes, to lag in the skin capillaries. As previously mentioned, the capillary count in patients with pernicious anemia who have not been treated is always greater than the venous blood count and is often more than 50 per cent greater. This condition gives rise to an unusually rosy color in the superficial tissues in patients with pernicious anemia, even when the capillary red count is reduced by one

or two million or more. In fact, a patient with pernicious anemia who has a capillary red count as low as three million, with the venous count much lower, may have normal or increased color both in the palms and in other surfaces. In pernicious anemia, therefore, one cannot interpret color according to the same rules as one does in persons with secondary anemia. In fact, in cases of pernicious anemia in which treatment

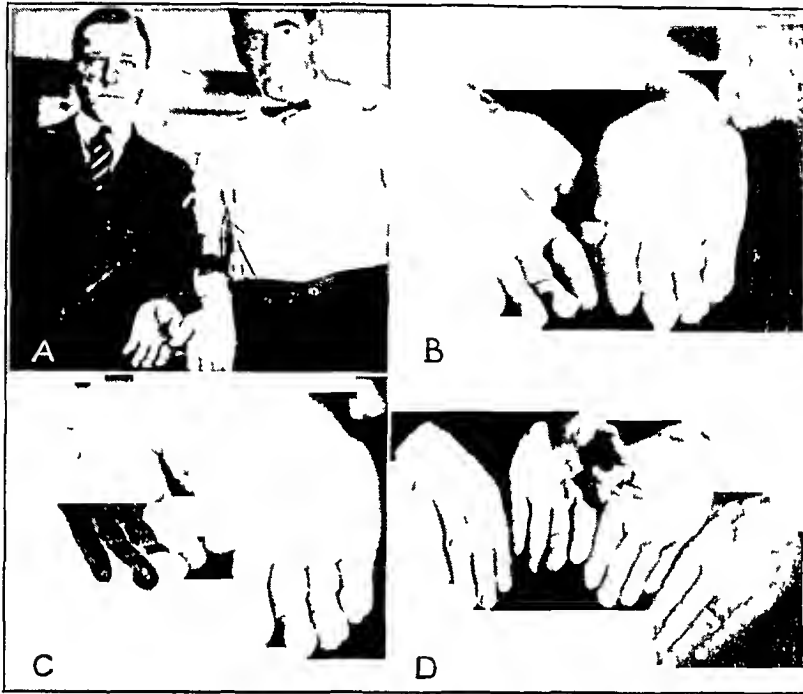


Fig 3—In *A*, the man on the right has a severe case of pernicious anemia, he weighs considerably over 200 pounds (99.7 Kg). The photographs were taken by ultraviolet light. Note the marked contrast between the pallor of the palm and the relatively normal color of the face, this is not rare in pernicious anemia. One could hardly detect anemia in this patient by examination of the skin or lips. The conjunctivae were pale and the palm of the hand appeared almost bloodless, the red cell count was 1,420,000, the hemoglobin, 30 per cent. *B* shows the palm after the introduction of 600 cc of blood by direct transfusion, the red count was 2,170,000. *C* was taken after the introduction of 600 cc of blood by direct transfusion. Note how little gain in the color of the palm has occurred after the introduction of this amount of blood. The red cell count was 2,860,000. *D* indicates the hands after the introduction of 500 cc of blood by direct transfusion, the red count was 3,200,000. Note that both the back and palm of the hand approximates normal in the photograph. There was in reality a marked difference between the real color of the palm and the normal which is not shown in the photograph. Note how deceptive a comparison of the backs of the hands may be, the anemic patient shows more color than the normal. An additional 500 cc of blood was required to restore a satisfactory color. The patient left before complete blood examinations and photographs could be made. Note also that color does not appear after the first transfusions but appears quickly as blood volume approaches normal, this is the rule. In one person (not illustrated), four donors were used before any noteworthy change in the color of the palm was visible. Two donors used subsequently, especially the second one, restored the color of the palm to normal with great rapidity.



Fig 4—*A* shows the palm of a woman with pernicious anemia (on the right), her weight was about 85 pounds (38.6 Kg). The red count was 1,180,000, the hemoglobin, 50 per cent (taken by sunlight). *B* shows her palm after the introduction of 1,200 cc of blood, the red cell count was 3,370,000, the hemoglobin, 80 per cent. Note that in spite of the persistent low red cell count, the color was restored to about normal.

The reproductions, especially of this illustration, are not as clear and distinct as might be desired, and do not adequately illustrate the condition under discussion.

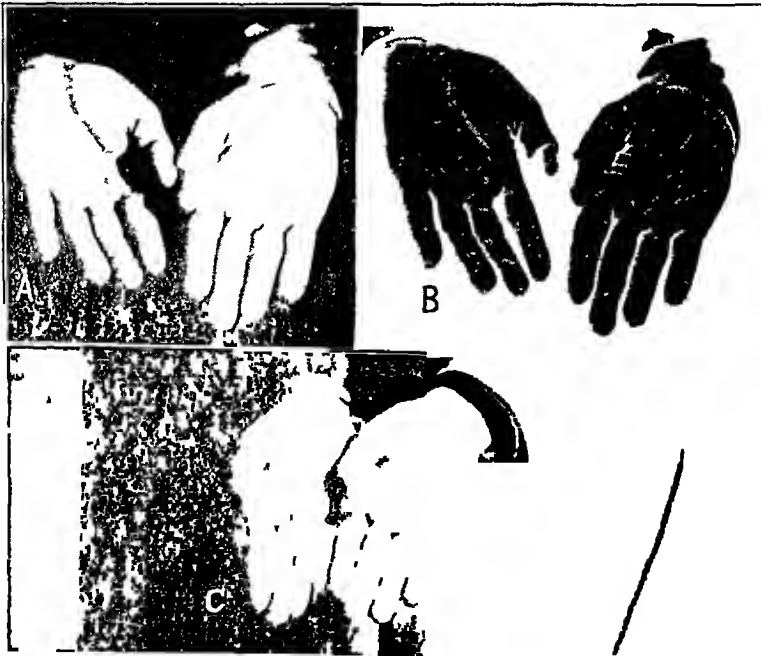


Fig 5—*A* shows the palm of a man with secondary anemia (on the right), his weight was 180 pounds (81.6 Kg), the red cell count, 3,490,000, the hemoglobin, 45 per cent. *B* shows the palm after the introduction of 1,700 cc of blood from three donors, the red cell count was 4,230,000. *C* indicates the same palm after the introduction of 600 cc of blood, the red cell count was 5,200,000, the hemoglobin, 80 per cent. The patient was subjectively normal.

has not been given, a red count exceeding three and one half million seems harmful to the patient in the presence of marked macrocytosis. The patient tolerates better a moderately reduced count with palms of normal color or slightly paler than normal. On the Minot and Murphy diet, the status changes. In successfully treated patients, macrocytosis becomes less marked, and capillary and venous counts may then run about parallel.



Fig 6—The palm of a man with a case of high grade plethora (right), his weight was in excess of 200 pounds (99.7 Kg). He gave a past history of having had nosebleed to the extent of from $1\frac{1}{2}$ to 3 pints on four separate occasions, each time with improvement in his general strength and a feeling of well being. A venous section had been performed on one occasion to the extent of 3 pints. He lost $7\frac{1}{2}$ pints a few days later from epistaxis following a nasal operation. He said that following this he never felt better in his entire life. Examination showed a picture of a highly plethoric person with a beefy-red appearance of the palms, as shown in the photograph. In spite of this, however, his red cell count was only 5,300,000 and the hemoglobin, 95 per cent. One pint of blood was withdrawn on each of two consecutive days with a change in the color of the palms to be noted in the figure on the right.

SUMMARY AND CONCLUSIONS

1 A slight or marked grade of either anemia or plethora can be diagnosed most readily, I believe, through a comparison of the color of the palm of the hand of the patient with that of a proved normal person according to a simple technic which has been described

2 The skin of the palm of the hand was chosen for making this comparison because under the usual conditions indoors, the color of the palm is remarkably constant in a given person. The color of the palm is believed to be more constant than the color of other surfaces, because of the fact that it is believed to take a smaller part in regulating the loss of body heat than other surfaces, and for this reason is not changed to any great extent through the effect of small differences in tempera-

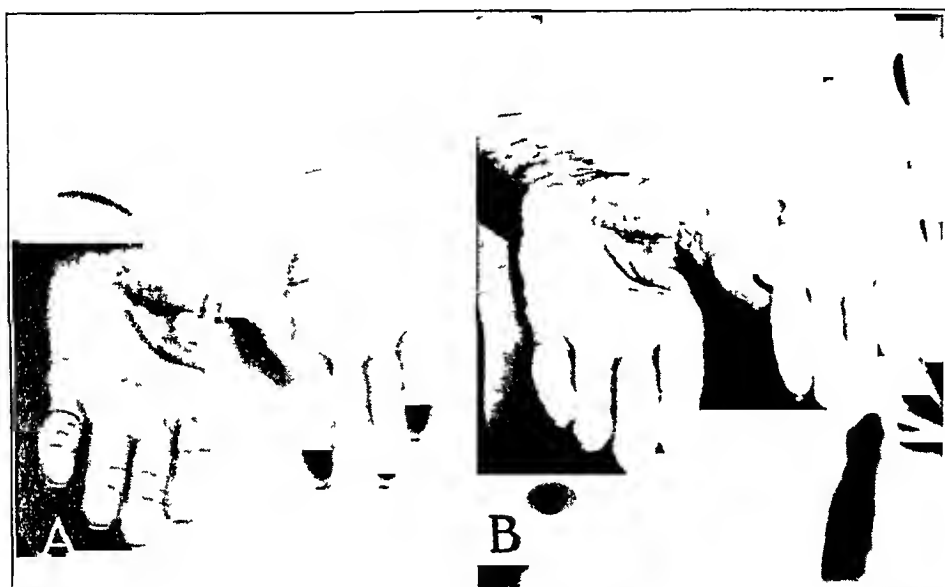


Fig 7—In *A* the palm on the left is that of a patient with true polycythemia and a red cell count of nearly 8,000,000. Contrast this with the plethoric person shown in the previous figure who had a red cell count scarcely exceeding 5,000,000. In *B*, note the paling of the palm following the withdrawal of 2,000 cc of blood in divided doses. The red cell count was eventually reduced to nearly normal with marked improvement in health.

ture and exercise. It, furthermore, does not vary in color through the effect of emotional disturbances as does the skin of the face, nor does it vary in different normal persons to the same extent as does the color of the lips or nails. It seems better adapted, therefore, for the estimation of average color than other skin surfaces. Exceptions to this rule are mentioned in the text.

3 The palm of the hand is preferred, furthermore, because of the fact that if held at the level of the apex of the heart, the color is not modified by changes in the position of the patient. The color of

other surfaces, such as of the face or conjunctivae, is greatly influenced by a change from a standing to a lying posture

4 I have found after a large experience that the color of the palm is influenced by few conditions except anemia and plethora, and that from a comparison of the patient's palm with that of a normal person, one can demonstrate slight deviations from the optimum in the quantity of hemoglobin in the general circulation

5 Comparison of the palm of the patient's hand with that of a normal person during and after blood transfusion and during and after venous section is a most reliable guide when one wishes to decide whether or not an adequate amount of blood has been introduced or withdrawn

5 If the foregoing statements are true, anemia and plethora in slight grade are common conditions

7 Physicians who study carefully the color of the palm of the hand on a number of patients according to the technic described, and who keep in mind the exceptions mentioned in the text, will find they have a simple, accurate and direct method of examination which can be used fearlessly in diagnosis

COMMENT

In presenting this paper I hope that my efforts are not misunderstood I am presenting a method for observing a patient's color, which I think is far more accurate and dependable than methods which have been used prior to this time I am not presenting a method for the estimation of blood volume or hemoglobin ratios

I believe, however, that through careful testing of a patient's color one can gain valuable information concerning the status of his blood, that is, whether the total quantity of hemoglobin in circulation is optimum for the patient, or too high or too low A patient's color does not depend wholly on his blood volume, his red count, the hemoglobin content of a unit of blood, or on the capacity of his vascular system in proportion to his needs His color depends rather on a mean between all these factors One gains a result, therefore, in testing color which can be obtained, I believe, in no other way and which is, I believe, an important procedure in studies of anemia and plethora It gives the same impression that physicians have gained through centuries of time by examination of the color of the conjunctivae, lips, nails and other parts of the body except that it is gained through the use of a method which is evidently much more accurate and dependable

THE PARATHYROID GLANDS

THEIR RELATIONSHIP TO THE THYROID, WITH SPECIAL REFERENCE
TO HYPERTHYROIDISM *

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The purpose of this paper is to discuss some of the literature dealing with the thyroid-parathyroid relationship and to present a few facts obtained by an analysis of over 550 determinations of the serum calcium in cases of disease of the thyroid gland. The work has been undertaken to determine, if possible, whether or not there is an actual antagonism between these two glands, as is believed by many authors. The practical value of such research lies in the fact that if such antagonism does exist, then the use of the active principle of the parathyroid glands, which can now be obtained, should be a useful adjunct in the treatment of patients with hyperthyroidism.

The parathyroid glands were first described by Remak¹ in 1855, and later, by Virchow² in 1863. The discovery of the parathyroid glands is rightly ascribed to Ivar Sandstrom³ who, in 1880, fully described them, and called attention to their anatomic and histologic significance. They were rediscovered by Gley⁴ in 1891. Since the publication of these and other early papers,⁵ more than 500 papers dealing with these glands have appeared. A cursory review of the literature suggests the possibility that a functional relationship exists between the thyroid and parathyroid glands.

EMBRYOLOGY

A few of the salient facts in regard to the embryology of these glands should be noted. The parathyroid bodies arise as two separate pairs, superior and inferior. The inferior pair, which finally lies behind the inferior borders of the lateral lobes of the thyroid, arises from the third branchial cleft. The superior pair, which finally lies near or on the central or upper part of the dorsal surfaces of the lateral thyroid lobes, arises from the fourth branchial cleft.

Many authors claim that the thyroid arises in part from two lateral bodies which are outgrowths of the posterior wall of the fourth branchial

* From the Cleveland Clinic, Cleveland

1 Remak, R. Untersuchungen über die Entwicklung des Wirbelthieres
35 194, 1851

2 Virchow. Die krankhaften Geschwülste 3 13, 1863

3 Sandstrom, I. Upsala Lakaref. förh. 15 441, 1880

4 Gley, E. A. Compt. rend. Soc. de biol. 3 843, 1891

5 Kadyi, A. Arch. f. Anat. u. Entwicklungsgesch., 1879, p. 312. Madelung, O. W. Arch. f. klin. Chir. 24 71, 1879. Millzner, R. J. Occurrence of Parathyroid on Anterior Surface of Thyroid Gland, J. A. M. A. 88 1053 (April 2) 1927

cleft The majority of authors agree, however, that the origin of the thyroid is solely from a median body at the root of the tongue

ANATOMY

Gross—The two pairs of glands mentioned are considered the normal number, yet the so-called accessory parathyroid glands have been recognized for many years Millzner⁶ reported the recognition of parathyroid glands in the human body, on the anterior surface of the thyroid in 12.9 per cent of the 162 specimens which had been removed at thyroidectomy In the dissections in the clinic, the presence of parathyroid glands has been noted frequently The number of cases in which this condition has been seen is not large enough to justify a statement as to the percentage of incidence, but it is thought that it occurs frequently because of the deformity of the lateral lobes in cases of adenoma

The size of the parathyroid glands varies greatly, the glands ordinarily being small flattened ovoid bodies lying in the areolar tissue on the surface of the thyroid gland, which measure from 3 to 14 mm in length and from 1 to 3 mm in breadth and thickness

The cut surface of the glands varies from a yellowish or a grayish-brown to a cocoa color

The blood supply of the parathyroid glands is derived for the most part from the inferior thyroid artery Many glands, lying on the capsule of the thyroid, especially those on the anterior surface, are directly connected with the thyroid capsule by at least one distinct vessel, moreover, according to the statement of Sacerdoti,⁷ the nerve supply is also furnished by the nerves of the thyroid gland Anderson⁸ found that after these nerves pass through the parathyroid capsule, they terminate within the epithelium of each glandule

Microscopic—Each gland possesses a capsule of fibrous connective tissue which sends branches into the gland substance, carrying the blood vessels and dividing the parenchyma into bands and clumps of cells of two main types (*a*) the chief cells, which are large polygonal cells, characterized by a clear cytoplasm and faintly staining nucleus, and (*b*) the oxyphil cells, which are much less numerous The cytoplasm of these cells stains strongly with eosin, and the nucleus, with hematoxylin

A so-called "frothy" cell has also been described Small irregular vesicles which may or may not contain colloid are frequently seen

Comparative—Parathyroid glands have been recognized in all classes of vertebrates with the exception of fishes⁹ A failure to recognize the

⁶ Millzner, footnote 5 (third reference)

⁷ Sacerdoti Internat Monatschr f Anat u Physiol **11** 326, 1894

⁸ Anderson, O A Arch f Anat u Entwcklungsgesch, 1894, p 225

⁹ Cowdry, E V, in Barker, L Endocrinology and Metabolism, New York, D Appleton & Company, 1922, vol 5, p 501

importance of the anatomic arrangement of these glands in mammals affords an explanation for many of the contradictory results obtained by many of the earlier investigators in this field. In the dog and the cat, the parathyroid and thyroid glands are so closely associated that all the parathyroid glands are removed at thyroidectomy, whereas in the rabbit only the superior, or so-called internal pair, are removed. It is interesting to note that although these glands are usually histologically distinct, the association may be so close that it is difficult to know whether the structure is the thyroid or parathyroid gland. Ochsner and Thompson¹⁰ stated that in some birds the parathyroid tissue is directly continuous with the thyroid, not even being separated from it by a septum but forming a single gland, while in others, the anatomic thyroid is entirely like the parathyroid in microscopic appearance.

EXTIRPATION EXPERIMENTS

Hypertrophy of One Set of Parathyroid Glands After Removal of Another Set—Walbaum,¹¹ Erdheim¹² and Pepere¹³ failed to observe an appreciable increase in the size of the internal parathyroid glands in rabbits after removal of the external glands, although it has since been shown by Haberfeld and Schilder¹⁴ that there is a marked degree of hypertrophy of the internal parathyroid glands in these animals, if, in addition to the external parathyroids, the accessory glands situated on or about the thymus are also removed.

Hypertrophy of the Parathyroid Glands After Thyroidectomy—Gley⁴ held at first that the parathyroid bodies are made up of embryonal thyroid tissue and that they assume the function of the thyroid gland after that organ has been removed. This view has not been substantiated, on the contrary, Gley himself, in association with Nicolas,¹⁵ repeated his experiments and was forced to abandon this view.

Vincent and Jolly¹⁶ have described structural changes in the parathyroid glands of cats following thyroidectomy. Their experiments, however, have never been substantiated.

In many cases, Biedl¹⁷ found that the removal of the thyroid together with the parathyroid interna is almost always associated with hyper-

10 Ochsner, A. J., and Thompson, R. L. *The Surgery and Pathology of the Thyroid and Parathyroid Glands*, 1910, p. 226.

11 Walbaum. *Mitt a d Grenzgeb d Med u Chir* **13** 298, 1903.

12 Erdheim, J. *Beitr z path Anat u z allg Pathol* **33** 158, 1903.

13 Pepere, A. *Arch de med exper et d'anat path* **20** 21, 1908.

14 Haberfeld, W., and Schilder, C. *Mitt a d Grenzgeb d Med u Chir*, 1909, vol. 29.

15 Gley, E., and Nicolas, A. *Compt rend Soc de biol*, 1895, p. 216.

16 Vincent, S., and Jolly, W. A. *J Anat & Physiol*, 1895, vol. 32.

17 Biedl, A. *The Internal Secretory Organs*. London, John Bale, Sons and Danielsson, 1913, p. 52.

trophy of the parathyroid externa, the amount of hypertrophy bearing a direct relation to the length of time after operation. The parathyroid glands of a growing dog one year after thyroidectomy were found to be twice as large as those of controls of the same litter.

Hypertrophy of the Thyroid After Parathyroidectomy—Hypertrophy of the thyroid following parathyroidectomy has been reported by Edmunds,¹⁸ Lusena,¹⁹ Vassale and Generali,²⁰ Halpenny and Thompson²¹ and others. These experiments seem to support strongly the possibility of a functional antagonism between these glands.

THE EFFECT OF FEEDING THYROID EXTRACT ON THE FUNCTION OF THE PARATHYROID GLANDS

In her experiments on the thyroid, Kunde²² noted that the administration of thyroid extract exerted a definite influence on the control of tetany in a thyroparathyroidectomized dog in a tetanoid state. In the case of a dog which had previously required from 1 to 1.3 Gm of calcium lactate per kilogram of body weight per day for the control of tetany, the calcium was discontinued on the eleventh day during the time of thyroid extract feeding, when signs of hyperthyroidism were present. During the following three months, the administration of thyroid extract was continued and there was no recurrence of tetany. The author fails to state, however, whether or not the tetany could be made to recur by the discontinuance of the thyroid extract.

The beneficial results obtained by the administration of thyroid extract to animals with tetany has been observed by other authors, and it is generally conceded that animals with tetany die in a shorter time when they are not given thyroid extract.

Kocher formerly used large doses of thyroid extract and iodothylin in cases of postoperative tetany, apparently with beneficial results. For many years, Cile has used thyroid extract together with parathyroid extract in the treatment of subjects with postoperative tetany. It must be noted, however, that in these cases there was a coexisting disturbance in the function of both the thyroid and parathyroid glands.

It is interesting to note in this connection that Cameron and Carmichael caused deaths from tetany by feeding thyroid extract to rats. They did not consider, however, that this was a true parathyroid tetany, but that death was probably due to tetany caused by hyperpnea.

18 Edmunds, W. J. *Path & Bact* **12** 101, 1907-1908

19 Lusena, G. *Studio critica sperimentale*, 1899

20 Vassale, G., and Generali, F. *Arch ital de biol* **33** 154, 1900

21 Halpenny, J., and Thompson, F. D. *Anat Anz* **34** 376, 1909

22 Kunde, Margaret M. *Am J Physiol* **82** 195 (Sept.) 1927

In this connection, a case cited by Percival and Stewart²³ is interesting. A cretin, in whom the serum calcium was 9.9 mg per hundred cubic centimeters, was fed thyroid extract. The basal metabolism rose from -5 to $+37$ per cent in three days, the serum calcium remaining 9.9 mg. In twenty-four days, the basal metabolism had risen to 79 per cent and the serum calcium was 13.2 mg. Withdrawal of thyroid extract for fourteen days was accompanied by a fall in serum calcium to 9.6 mg.

THE EFFECT OF THE ADMINISTRATION OF PARATHYROID EXTRACT ON THE FUNCTION OF THE THYROID GLAND

Moussu²⁴ found that the administration of parathyroid extract to horses had an unfavorable action in cases of myxedema, but was beneficial in cases of hyperthyroidism. He concluded that the hyperfunction of the thyroid was restrained by the parathyroids.

Mandelstamm²⁵ reported the production of exophthalmos in rabbits by injections of parathyroid extract, an observation entirely contradictory to the work of Moussu. Mandelstamm expressed the opinion that the exophthalmos is due to increase in the activity of the thyroid gland. This conception is strengthened by Kunde's²² observation that it is possible to produce marked exophthalmos in rabbits by administering thyroid extract.

It must not be forgotten, however, that previous to the isolation of the active principle of the parathyroid glands by Collip, the administration of parathyroid extract had never been on a satisfactory basis. Clinically, however, I believe that parathyroid extract has a weak though definitely positive effect.

THE STRUCTURE OF THE THYROID AFTER ADMINISTRATION OF PARATHYROID EXTRACT AND OF THE PARATHYROID GLANDS IN HYPERTHYROIDISM

Large doses of parathyroid extract have been given to rats by Cameron and Carmichael²⁶ who failed to observe any consequent changes in the thyroid gland.

Kurokawa²⁷ produced hyperparathyroidism in 180 rats by transplantation of parathyroid glands. In forty-eight patients in whom the glands were proved microscopically to have remained alive, there were generalized atrophic changes in body tissues, the thyroid being no exception.

23 Percival, G. H., and Stewart, C. P. *Quart J Med* **19** 235 (April) 1926.

24 Moussu, G. *Compt rend Soc de biol* **6** 242, 1899.

25 Mandelstamm, M. *Ztschr f d ges exper Med* **35** 370 1923.

26 Cameron, A. T., and Carmichael, J. *Am J Physiol* **58** 1 (Nov) 1921.

27 Kurokawa, K. *Japanese M World* **5** 241, 1925.

MacCallum²⁸ reported the structure of the parathyroid glands in cases of hyperthyroidism. He noted several changes but, in general, the parathyroid tissue was said to be normal. Benjamins²⁹ reported a similar observation. Structural changes, such as the increase of intraglandular connective tissue or the formation of glandlike hollows filled with colloid, have been reported in cases of hyperthyroidism. Kuio-kawa,²⁷ who studied the structure of 815 parathyroid glands in many conditions, found that these changes were frequent, however, he did not report the structure in any cases of hyperthyroidism.

I have made a microscopic study of fourteen parathyroid glands in cases of hyperthyroidism. Three of the specimens were from three patients who died from acute hyperthyroidism. In two of the cases operation had not been performed, and in one acute case hyperthyroidism developed one month after the ligation of the superior thyroid arteries. Observation did not reveal any constant change in these glands.

TETANY AND ENDEMIC GOITER

McCarrison³⁰ stated that in certain parts of India the mothers of cretins and of children born with goiter commonly suffer from tetany during pregnancy. A case has been cited in which tetany developed during pregnancy in a woman with goiter who lived in a district in which endemic goiter was common. When the patient moved to a nongoitrous district, the tetany disappeared, reappearing again, however, after she had returned to the former locality.

THE FUNCTION OF THE PARATHYROID GLANDS AND A METHOD OF MEASURING IT

Ever since it has been known that the extirpation of the parathyroid glands is associated with tetany, much of the study of the function of the parathyroid glands has centered about experimental tetany. This condition has been produced by many methods besides parathyroidectomy, among which are the following: (1) voluntary hyperpnea,³¹ (2) precipitation of calcium in the tissues,³² (3) the intravenous administration of large doses of sodium chloride,³³ (4) intravenous administration of sodium bicarbonate,³⁴ (5) intravenous administration of neutral or

28 MacCallum, W. G. *Brit. M. J.* **2** 1282, 1906.

29 Benjamins, C. E. *Beitr. z. path. Anat. u. z. allg. Pathol.* **31** 143, 1902.

30 McCarrison, R. *Lancet* **1** 817, 1913.

31 Collip, J. B., and Backus, P. L. *Am. J. Physiol.* **51** 568 (April) 1920.

32 Loeb, J. *Am. J. Physiol.* **5** 362, 1901.

33 Greenwald, I. *Am. J. Physiol.* **28** 103, 1911.

34 Harrop, G. A. *Bull. Johns Hopkins Hosp.* **30** 62 (March) 1919.

alkaline phosphates,³⁵ and (6) the administration of guanidine or the more toxic methyl-guanidine³⁶

A great deal of confusion has arisen as to the actual cause of tetany, and many theories have been advanced, some of the more important of these being the following

1 The liver plays a rôle of primary importance³⁷

2 The symptoms are due to the absorption of products of bacterial decomposition from the intestine³⁸

3 The theory advanced by Wilson³⁹ and his co workers is that a derangement of the acid-base equilibrium is the actual cause of the symptoms

4 The theory that was first advanced by Vassale and Generali is that the products formed by the metabolism of the thyroid are neutralized by the action of the parathyroid gland. These authors believed that more severe tetany resulted from parathyroidectomy alone than from thyroparathyroidectomy, but other authors have not agreed with their view, nor with that of Rudinger⁴⁰ who held a somewhat similar view regarding thyroid-parathyroid balance

5 A theory which has been widely held was first advanced in 1912 by Koch⁴¹. This is the so-called guanidine intoxication theory, which is based on the presence of methyl-guanidine and other bases in the urine following parathyroidectomy. Paton,³⁶ who has been the chief advocate of this theory, expressed the belief that tetany is due to a definite toxemia and that the secretion of the parathyroid glands controls the toxemia by the regulation of the production and destruction of guanidine and methyl-guanidine. Paton makes the following claims: 1 The symptoms produced by the administration of guanidine and methyl-guanidine are identical with those in cases of postoperative tetany. 2 Small doses of these substances markedly aggravate the symptoms of tetany. 3 The amount of these agents in the blood and in the urine is increased after parathyroidectomy.

Findlay and Sharpe⁴² and Nattrass and Sharpe⁴³ observed an increase in the amount of guanidine in the urine in cases of tetany. The

35 Binger, C. *J Pharm & Exper Therap* **10** 105 (Aug) 1917

36 Paton, N. *Edinburgh M J* **31** 541 (Oct) 1924

37 Blumenstock, J., and Ickstadt, A. *J Biol Chem* **61** 91 (Aug) 1924

38 Dragstedt, L. R., and Peacock, S. C. *Am J Physiol* **64** 424 (May) 1923

39 Wilson, D. W., Sterns, T., and Thurlow, M. *J Biol Chem* **23** 89, 1915

40 Rudinger, C. *Ergebn d inn Med u Kinderh*, 1908, p 221

41 Koch, W. F. *J Biol Chem* **12** 313, 1912

42 Findlay, L., and Sharpe, J. S. *Quart J Med* **13** 433 (July) 1920

43 Nattrass, F. J., and Sharpe, J. S. *Brit M J* **2** 238 (Aug 13) 1921

guanidine theory is strongly supported by Frank, Stern and Nothmann,⁴⁴ Gyorgy and Vollmer,⁴⁵ Palladin and Grilliches⁴⁶ and others

It is also claimed by Watanabe⁴⁷ and others that there is a direct relationship between the injection of guanidine and the level of calcium in the blood. Nelken,⁴⁸ Salvesen⁴⁹ and Collip and Clark⁵⁰ failed to confirm this opinion.

The one outstanding fact which has been established as evidence against the guanidine theory is that Collip and Clark observed guanidine intoxication in the presence of an overdosage of parathyroid hormone, that is, hypercalcemia fails to control tetany from guanidine poisoning while it is incompatible with tetany following parathyroidectomy.

A method for estimating the activity of the parathyroid glands based on guanidine destruction was advanced in 1923 by Vines,⁵¹ and was found by White and Cameron⁵² to have negligible activity when tested with Collip's active parathyroid extract.

6 The calcium theory of the function of the parathyroid gland was advanced in 1909 by MacCallum and Voegtlin,⁵³ and was confirmed in 1923 by Salvesen,⁴⁹ who expressed the belief that the parathyroid glands control the calcium content of the blood. In 1924, Greenwald⁵⁴ stated that there are only two well-authenticated metabolic changes after parathyroidectomy, one is the lowered calcium content of the blood serum, and the other, the diminished excretion of phosphorus in the urine.

In his recent work, Collip⁵⁵ has proved conclusively that the outstanding function of the parathyroid glands is their specific effect on the concentration of calcium in the blood. It appears now to be established that the activity of the parathyroid glands can be measured to a great extent by the level of the blood calcium.

That it may not, however, be possible to make serum calcium an absolute gage of the degree of activity which is indicated by clinical observations is suggested by the following reported cases

44 Frank, E., Stern, R., and Nothmann, M. *Ztschr f d ges exper Med* **24** 341, 1921.

45 Gyorgy and Vollmer. *Arch f exper Path u Pharmacol* **105** 200, 1922.

46 Palladin, A., and Grilliches, L. *Biochem Ztschr* **146** 458, 1924.

47 Watanabe, C. K. *J Biol Chem* **36** 531 (Dec.) 1918.

48 Nelken. *Ztschr f d ges exper Med* **32** 343, 1923.

49 Salvesen, H. A. *J Biol Chem* **56** 443 (June) 1923.

50 Collip, J. B., and Clark, E. P. *J Biol Chem* **67**:21 (March) 1926.

51 Vines, H. W. C. *Brit M J* **2**:559 (Sept.) 1923.

52 White, F. D., and Cameron, A. T. *Tr Roy Soc Can* **19** 45, 1925.

53 MacCallum, W. G., and Voegtlin, C. *J Exper Med* **11** 118, 1909.

54 Greenwald, I. *J Biol Chem* **59** 329, 1924.

55 Collip, J. B. *Medicine* **5** 1, 1926.

Within the last year, three cases of mild chronic tetany in which the blood calcium is within normal limits, have come to my notice. Surgical measures had not been employed on any of the three patients, all of whom were women between 30 and 40 years of age. None of them had goiter, nor were they pregnant. One showed nervous excitability, with twitching of the muscles of the forearm, occasionally accompanied by slight pain. These symptoms had been present almost daily for four months. The second and third patients complained of slight numbness and tingling of the fingers and small, painless, cramplike contractions of the muscles of the fingers; in one patient, the muscles of the forearm were occasionally affected. The symptoms had been present for eight and two weeks, respectively. The first patient was seen in March, 1927, and the other two in September, 1927. In none of the patients was there a positive Chvostek's nor Trousseau's sign present, and the serum calcium was normal in all three. These patients were all given parathyroid extract, 0.2 grains (0.01296 Gm.) three times daily for a period of two weeks, with the results that the symptoms entirely disappeared. The first patient had slight symptoms for ten days, the symptoms of the other two completely disappeared in four and seven days, respectively.

In the patient who was seen in March, recurrence of the symptoms was not noted when she was again observed three months later. The second patient was free from symptoms one month after the treatment had been discontinued, and the third patient has not been heard from since two weeks after the completion of the course of treatment with thyroid extract. Although there may have been some doubt as to the diagnosis, the symptoms were suggestive and disappeared on treatment.

Another condition opposite to the foregoing one may occur. Patients with definite chronic postoperative tetany may be free from symptoms while the serum calcium remains about 8 mg. per hundred cubic centimeters, or slightly above this level, whereas if it falls below 8 mg., the definite classical symptoms occur. All who are familiar with chronic postoperative tetany have undoubtedly frequently observed this sequence of events.

A third group of cases shows that symptoms of tetany may remain for several days after the serum calcium has returned to the normal level. This condition may, however, be due to the fact that although the serum is normal, the amount in the tissues is still slightly deficient. A case seen recently will illustrate this point.

A married woman, aged 37, had had a thyroidectomy for hyperthyroidism. On the morning of the fourth day after operation, she complained of numbness of the fingers and toes and stiffness of the fingers. She showed a mild degree of carpal spasm and a moderately marked Trousseau's sign. The calcium was 7.9 mg. per hundred cubic centimeters. Two cubic centimeters of parathyroid extract-Collip (Lilly) was given subcutaneously and the symptoms promptly subsided. Because of the presence of mild symptoms, 1 cc. of parathyroid extract-Collip was given on the fifth, sixth, and seventh days after operation. The level of the calcium rose to 10.4 mg. and further medication was not given. On the eighth day after operation, when the serum calcium was 10.3 mg., the patient described a sensation of stiffness and slight numbness in the fingers. The following day, she said that her

fingers felt "as though they had just been asleep," the serum calcium being 10.8 mg. On the tenth day, she described a slight tingling of the fingers as though "they had been cold and were just getting warm again." The serum calcium on this day was 10.5 mg. The symptoms had entirely disappeared on the eleventh day after operation and they did not recur during observation through the following week.

These observations suggest that the smaller changes in the function of the parathyroid glands cannot always be detected by changes in serum calcium, however, I believe that it is the best method available.

THE BLOOD CALCIUM IN HYPOTHYROIDISM AND HYPERTHYROIDISM

In the literature may be found many references to the level of serum calcium in cases of hypothyroidism and hyperthyroidism. Hall⁵⁶ stated that the content of this salt in the blood is diminished in both conditions.

Herzfeld and Neuberger⁵⁷ reported determinations of the serum calcium in nineteen cases of hyperthyroidism. In one third of these cases, the level was normal, and in two thirds, it was either above or below normal.

In a study of blood calcium levels in twenty-six cases in which thyroidectomy was performed, Rabinowitch⁵⁸ noted a constant drop following operation. Neither symptoms of tetany nor any parathyroid tissue was found in the operative specimen of any of the cases. He assumed the cause of the diminished serum calcium to be trauma of the parathyroid glands caused by manipulation.

In the experiments reported in this paper, the serum calcium has been measured in cases of hypothyroidism and hyperthyroidism. Cases in which there were symptoms of tetany have not been included.

The method used was a modification of the Kramer-Tisdall method, the permanganate solution being 0.01 normal. By this method, it may be noted that when one uses 2 cc. of serum an error of 0.4 mg. per hundred cubic centimeters will be made by an error of one drop of fluid in titrations. I have tried to have the titrations correct to one half of a drop in all experiments. Duplicate determinations were done in twelve cases, and the greatest difference found between two determinations on the same serum was 0.4 mg. This difference was found in two of the twelve cases. In one, there was a difference of 0.3 mg., in four, a difference of 0.2 mg. The results were identical in five.

The normal level of serum calcium was considered by Kramer and Tisdall⁵⁹ to be from 9.5 to 10.5 mg. per hundred cubic centimeters.

56 Hall, S. H. *Med. Press* **119** 436, 1925.

57 Herzfeld, E., and Neuberger, J. *Deutsche med. Wchnschr.* **1** 1324, 1875.

58 Rabinowitch, I. M. *J. Lab. & Clin. Med.* **9** 543 (May) 1924.

59 Kramer, B., and Tisdall, F. F. *J. Biol. Chem.* **47** 475, 1926.

Kramer and Howland⁶⁰ reported a normal variation of from 9.3 to 9.9 mg. Watchorn⁶¹ considered the range from 10 to 10.8 mg. to be normal, and Schamberg and Brown⁶² cited normal cases with a variation of from 9.7 to 11.3 mg. I have considered the extreme normal range of serum calcium to be from 9 to 11 mg. per hundred cubic centimeters.

EXPERIMENTAL WORK

In the first experiment, ninety-six determinations of the serum calcium were made in twenty-seven cases of hyperthyroidism in which bilateral ligation of the superior thyroid artery was performed. The results in this group of determinations are shown in chart 1. The ligations in each case were three days apart and determinations of the serum calcium were not made on the intervening days.

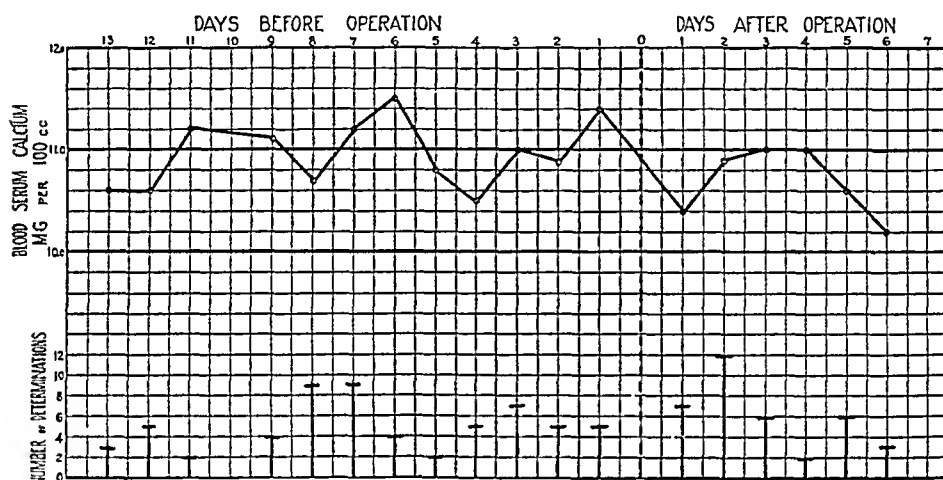


Chart 1—The relationship between ligation of the superior thyroid arteries and the blood serum calcium—ninety-six determinations in twenty-seven cases. The ordinates represent the serum calcium in milligrams per hundred cubic centimeters, the deep black lines, the number of patients on whom determinations were made on a given day, the abscissae, days before and after operation. Minus one (—1) means one day before the first ligation, and plus one (+1), one day after the second ligation.

It will be noted that definite changes in the serum calcium level did not result from this operation. Of the sixty determinations which were made before operation, the average value was 10.9 mg., while the average value in thirty-six determinations following these operations was 10.8 mg. per hundred cubic centimeters.

⁶⁰ Kramer, B., and Howland, T. *J. Biol. Chem.* **43**: 35 (Aug.) 1920.

⁶¹ Watchorn, E. *Quart. J. Med.* **18**: 288 (April) 1925.

⁶² Schamberg, J. F., and Brown, H. *Inorganic Salts in Blood as a Measure of Liver Damage in Treatment with Arsphenamines*, *Arch. Dermat. & Syph.* **9**: 368 (March) 1924.

In the second experiment, thirty-five determinations of the serum calcium were made in eighteen cases of hyperthyroidism in which lobectomy was performed. In 59 per cent of the cases, a fall in serum calcium followed this operation, the lowest levels occurring from the fourth to the sixth day after operation. Of twenty determinations made before operation, the average level was 10.8 mg, while of fifteen postoperative determinations, the average value was 10.5 mg, an average fall of 0.3 mg.

In the third experiment, 177 serum calcium values were established in 54 cases of thyroidectomy. A fall in serum followed this operation in 76 per cent of the cases. The average results in these cases are shown in chart 2. The average calcium level in ninety-one determinations

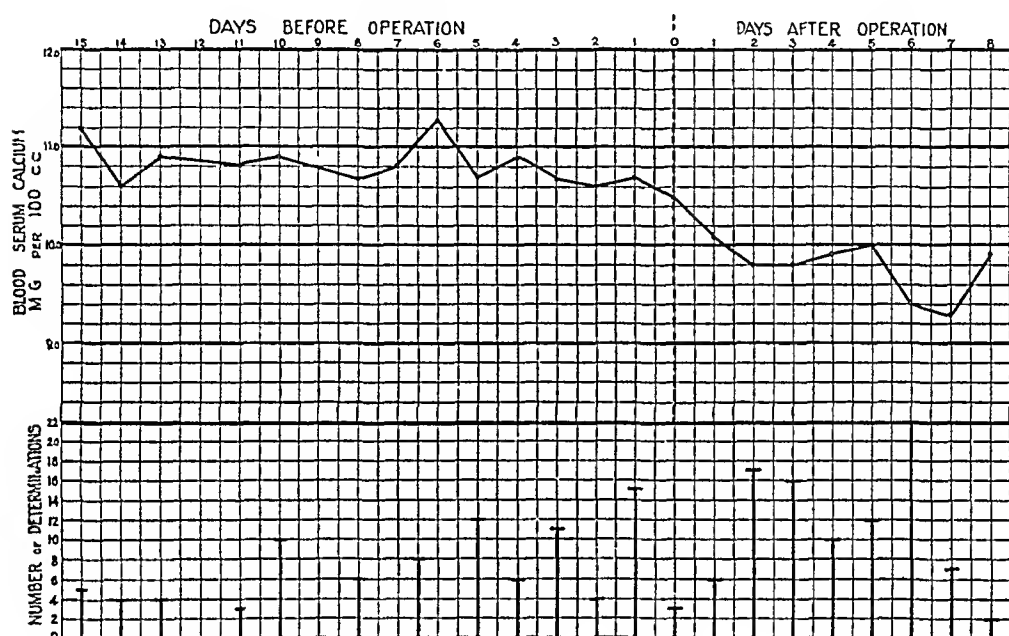


Chart 2—The effect of thyroidectomy on blood serum calcium in 177 determinations in 54 cases. The numbers represent the averages of the serum calcium levels in several cases on the same day relative to the operation. The black upright lines represent the number of cases on which determinations were made on a given day.

made before operation was 10.7, while the average of eighty-six determinations made after operation was 9.7, an average fall of 1 mg.

In 75 per cent of the cases, the fall was definite from the first to the eighth day after operation.

The fourth experiment includes 139 serum calcium levels in as many cases in which the basal metabolic rate was determined coincidentally, the blood for the test being taken in every case in the morning before the ingestion of food and within one hour after the metabolism test. Chart 3 has been compiled in the same manner as the two preceding charts, the abscissae here representing the basal metabolic rate

All calcium levels in cases in which the metabolic rates were within 5 per cent of one another have been averaged and plotted as one point. The metabolic rates varied from -30 to $+75$ per cent. The chart shows that there has been neither a definite rise nor fall in serum calcium in either hypothyroidism or hyperthyroidism. The average serum calcium in thirty-two cases, in all of which the basal metabolic rate was below zero, was 10.9 mg per hundred cubic centimeters. The average serum calcium in 105 cases, in which the basal metabolic rate varied from 0 to $+75$, was 11 mg per hundred cubic centimeters.

In 51 per cent of all cases, there was a hypercalcemia. This condition occurred evenly in hyperthyroidism and hypothyroidism in all cases in which a basal metabolic rate was determined.

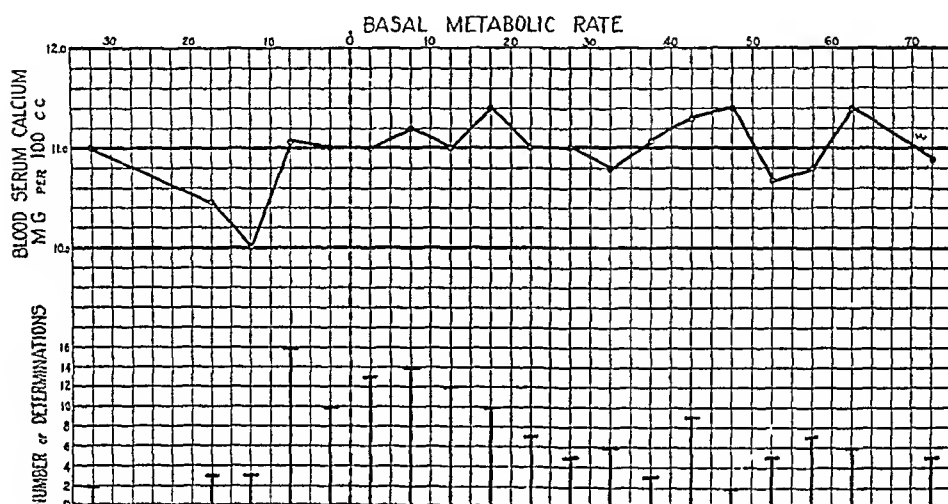


Chart 3—The relationship between the blood serum calcium and the basal metabolic rate in 139 cases. The abscissae represent the basal metabolic rate.

I consider that the fall in serum calcium which follows thyroid lobectomy and thyroidectomy is due to three main factors: (1) trauma which the parathyroid glands suffer from manipulation during operation, (2) disturbance in the blood supply of the parathyroid glands, from edema about the operative field, from direct trauma or infection, (3) the removal of parathyroid glands which have been on the anterior surface of the thyroid gland. In 1 per cent of all cases, hypocalcemia occurred, in each case it was present in a patient who was convalescing from thyroidectomy and with one exception it was found on the sixth or seventh day after operation.

SUMMARY

I have reviewed some of the more important articles dealing with the parathyroid glands and their relation to the thyroid. The points which seem of importance in regard to thyroid-parathyroid interrela-

tionship are 1 Hypertrophy of the thyroid or of the parathyroid glands may be provoked in either by the suppression of the other 2 Thyroid extract has been observed to have a beneficial effect in the treatment of the subjects with tetany 3 Definite changes in the parathyroid glands have not been found in hyperthyroidism

The function of the parathyroid glands has been measured by determinations of the serum calcium level In cases in which a ligation of the superior thyroid arteries was made, a definite drop in serum calcium did not occur A fall of this level was noted after lobectomy, and a much more marked fall occurred after thyroidectomy The serum calcium was found to be normal in 94 per cent of 139 cases of hypothyroidism and hyperthyroidism, and no relationship to the basal metabolic rate has been observed

In the experiments reported, I have found nothing to indicate an abnormal functioning of the parathyroid glands in either hypothyroidism or hyperthyroidism except in cases in which there has been actual trauma or removal of these glands I have not found any indication for the use of parathyroid hormone in cases of hyperthyroidism

PANCREATIC FUNCTION

II THE PANCREATIC ACTIVITY IN DIABETES MELLITUS*

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In 1788, Cawley¹ reported an intimate relationship between the sugar-regulating function and the pancreas and considered pancreatic disease an important factor in the etiology of diabetes. This was confirmed by various workers, such as Bright, Bouchardat, Friedreich, Bamberger, Fierichs, Senator, Seegen and others. The reports, however, were not more than statistical statements until Lancéreaux (1877), on the basis of many clinical and anatomic observations, described a special form of diabetes called *diabète pancréatique* or *diabète maigre*. This form is characterized by a sudden onset, a malignant course and a special tendency to the complication of tuberculosis. The epoch-making discovery of von Mering and Minkowski² in 1889, as well as the independent observations of N. de Dominicis,³ that complete extirpation of the pancreas in dogs always caused pronounced glycosuria, had made a marked effect on the development of the investigation of diabetes. Following the suggestion of Lancéreaux, Bouchard and Gilbert in France, diabetes has been classified anatomically into pancreatic, hepatic and nervous forms. As to the histologic alterations in the pancreas, opinions diverged at first. Some authors, such as Lépine and Lemoine, thought that the lesion of the acinous cells was the predominating feature, while many others, especially after the work of E. L. Opie, directed their attention to the insular involvement. The typical pathologic process of the disease was first noted by Opie⁴ in 1901, and later by Weichselbaum

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1 Cawley, cited by Labbe and Rechart. *Les troubles de la sécrétion externe du pancréas dans le diabète sucré*, Arch. d. mal. d. l'app. digestif **16** 867, 1926.

2 Von Mering, J., and Minkowski, O. *Diabetes nach Pankreasextirpation*, Zentralbl. f. klin. Med., 1889, p. 393, Arch. f. exper. Path. u. Pharmacol. **26** 371, 1889.

3 De Dominicis. *Studi sperimentali intorno agli effetti delle estirpazione del pancreas*, Giorn. int. delle sc. med., 1889, p. 801.

4 Opie, E. T. *Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans of the Pancreas*, Bull. Johns Hopkins Hosp. **12** 263, 1901.

and Stangl,⁵ who described the hydropic degeneration and vacuolization of the cells of the islands of Langerhans

The obtaining of the pancreatic hormone from the wasted glands of animals by ligating the pancreatic duct according to the method of Banting,⁶ and the preparation of insulin from the islands of Langerhans of certain fish, in which they are separated from the zymogenous tissue, according to the method of Macleod,⁷ have removed all doubt as to the correctness of the theory concerning the islands of Langerhans. Thus, a deficiency of the internal secretion of the pancreas as the immediate cause of the glycosuria is incontestably proved, but the extent to which other organic functions are involved still remains a question. According to Allen,⁸ in most, if not in all, cases of diabetes mellitus, there must have been a preceding disease of the pancreas. This investigator expressed the opinion that such pancreatic disease usually involves damage to both the insular and the acinous cells. According to Joslin,⁹ although proof of the cause of the disease is still lacking, an antecedent pancreatitis would appear to be the most logical explanation.

In view of the foregoing data, it is evident that in diabetes mellitus, in addition to the known diminution of the internal secretion of the cells of the islands of Langerhans, there may also be abnormalities in the external secretory activity of the pancreas.

Okada¹⁰ reported, perhaps for the first time, that in severe cases of diabetes a small amount of trypsin is often found in the duodenal contents. Von Noorden¹¹ reported that in some cases of diabetes there was a diminution in the trypsin and lipolytic enzymes present in the duodenal fluid, notwithstanding the fact that the feces still remained normal. Katsch and Friedrich¹² found a significant decrease of trypsin and lipase in only one of five cases. Langanke¹³ examined four patients with severe diabetes and found that all of them showed remarkably low activity of trypsin and lipase while the amylolytic activity remained normal.

5 Weichselbaum, A., and Stangl, E. Zur Kenntnis der feineren Veränderungen des Pankreas bei Diabetes Mellitus, *Wien klin Wchnschr* **14** 968, 1901

6 Banting, F. G., and Best, C. H. The Internal Secretion of the Pancreas, *J. Lab. & Clin. Med.* **7** 251 (Feb.) 1922

7 Macleod, J. J. R. The Source of Insulin, *J. Metab. Research* **2** 149, 1922

8 Allen, F. M. The Pathology of Diabetes, *J. Metab. Research* **1** 165, 1922

9 Joslin, E. P. The Treatment of Diabetes Mellitus, ed. 3, Philadelphia, Lea & Febiger, 1923, p. 137

10 Okada, S. Ueber die Pankreassekretion bei Sekretionsstörungen des Magens, *Mitt. d. med. Fak. d. Kaiserl. Univ. z. Tokyo* **13** 157, 1914

11 Von Noorden. Die Zuckerkrankheit, ed. 7, 1915

12 Katsch, G., and Friedrich, L. v. Bauchspeichelfluss auf Aetherreiz, *Klin. Wchnschr* **1** 112, 1922

13 Langanke, E. Untersuchungen über die Fermente des Pankreas vor und nach Injektion von Aether ins Duodenum, *Klin. Wchnschr* **1** 1458, 1922

Jones, Castle, Mulholland and Bailey¹⁴ made a comprehensive report on the pancreatic and hepatic activity in diabetes mellitus. They examined an unselected group of sixty-eight diabetic patients for evidence of alteration in pancreatic or hepatic activity. They found a diminution in the activity of one or more of the pancreatic enzymes in nearly one half of their cases. The striking fact in these observations is that amylolytic activity was apparently diminished in only 9 per cent of the cases, whereas proteolytic activity and lipolytic activity showed definite reductions below the minimum normal level in over a third of the cases. The elimination of bile pigment in the duodenal contents was abnormally high in about three fourths of the cases. In nearly one third of the cases there were associated abnormalities of the enzymes and pigment. The enzymatic abnormalities are probably due to associated anatomic and functional changes in the acinar tissue of the pancreas. Undernutrition may play a part in the production of such changes, but it is not the sole cause. It is suggested that the diminution of enzymatic activity may result in disturbances due to improper digestion of fat and protein. Efficient insulin therapy, with its associated increase in food intake and improvement of tissue function, seems to be associated with a reduction in pancreatic and hepatic abnormalities. Acidosis produces a marked disturbance in the enzymatic activity in the pancreas and also in the function of the liver. The improvement in pancreatic and hepatic function, as measured by changes in the enzymatic activity and elimination of bile pigment, following recovery from acidosis, is striking, and illustrates the degree to which acidosis affects all bodily functions. Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19 per cent of the cases in this series. In adults, cholelithiasis is probably one of the most important etiologic factors in diabetes mellitus. Baigý,¹⁵ Labbé and Rechad¹⁶ also made examinations to determine the enzymatic activity of the duodenal content in cases of diabetes mellitus. Labbé and Rechad could not find normal enzymatic activity in any of their ten cases. They examined the proteolytic and lipolytic activity and found that both enzymes were insufficient in six cases, in three cases only the proteolytic was diminished, and in one case, only the lipolytic activity. The insufficiency of the external secretion of the pancreas is often not apparent clinically, but is revealed only in the laboratory examination, while in

14 Jones C M, Castle W B, Mulholland H B, and Bailey F. Pancreatic and Hepatic Activity in Diabetes Mellitus, *Arch Int Med* **35** 315 (March) 1925

15 Baigý, R. Insuffisance pancreatique externe chez les diabetiques, etudiee par l'evaluation de l'activite fermentaire dans le liquide duodenal, *These de Paris*, 1926

16 Labbe, M, and Rechad. Les troubles de la secretion externe du pancreas dans le diabete sucre, *Arch d mal d l'app digestif* **16** 865, 1926

some cases it is shown by the symptoms of indigestion and severely impaired regulation of metabolism of sugar. This is why the diagnosis of pancreatic diabetes should be made with caution. Hernando¹⁷ also found a diminution of the enzymatic activity of the duodenal fluid in a great many cases of diabetes. On the other hand, Isaac-Krieger¹⁸ did not find a diminution of the duodenal contents in seven cases. Deusch and Drost¹⁹ examined the enzymatic activity of the duodenal contents in ten cases of diabetes of various degrees of severity in persons of different ages and did not find any deviation from that in control persons. They expressed the opinion that disturbance of the external secretion of the pancreas in cases of diabetes is exceptional and only found in cases in which primary enterogenic involvement of the pancreas (pancreatitis, cysts or stone formation) or a universal pancreatic involvement (arteriosclerosis, syphilis) exists. From their results, they attempted to classify the diabetes as a primary, chiefly kryptogenetic diabetes affecting the islands of Langerhans and a secondary, symptomatic diabetes with pancreatic involvement. Kusnetzow and Michailowa²⁰ examined six cases of diabetes and found in four cases the tryptic and lipolytic activity distinctly diminished while amylolytic activity showed normal values. The two other cases were normal in all enzymatic activity.

The opinions of the aforementioned authors vary widely. Some consider that the enzymatic activity of the duodenal contents is always abnormal in diabetes, others, that it is never abnormal and still others noted, individually and collectively, every modification of point of view between the two extremes. This state of affairs shows that it is important to make more exact and careful examinations in order to solve this problem. It seems necessary to consider why this controversy arose. Certain factors in the cases examined, i.e., severity and duration of the disease, age, nutrition, etc., might have an influence on the results. The most important factor, however, seems to be the method employed. As we mentioned in our first paper, all quantitative tests applied hitherto meet theoretical as well as real objections. Therefore, we wish to publish the results we obtained by using our newly devised method,²¹ which might be considered for the first time as a quantitative test of the pancreatic secretion in its real meaning. This method was published in the first paper of this series.²¹

17 Hernando, cited by Deusch and Drost. *Klin Wchnschr* **6** 2180, 1927.

18 Isaac-Krieger, cited by Deusch and Drost. *Klin Wchnschr* **6** 2180, 1927.

19 Deusch, G., and Drost, E. *Innere und aussere Sekretion des Pankreas*, *Klin Wchnschr* **6** 2180, 1927.

20 Kusnetzow, N. W., and Michailowa, S. J. *Die Sekretionstatigkeit der Bauchspeicheldruse im Verlaufe von Erkrankungen der Digestionsorgane*, *Arch f Verdauungskr* **40** 41, 1927.

21 Okada, S., Sakurai, E., Imazu, T., and Kuramochi, K. *Pancreatic Function I. The Quantitative Estimation of the Pancreatic Secretion*, *Arch Int Med* **42** 270 (Aug) 1928.

CLINICAL MATERIAL

The cases under consideration consisted of an unselected group of twenty-one patients with diabetes mellitus taken from the wards of the University Hospital of Tokyo. The youngest patient was 28 years of age, the oldest, 72. The average age was 45 years. Of the twenty-one patients, two-thirds were over 40 years of age and five over 50. There was a pronounced preponderance of the cases in men, sixteen being in men and five in women. The average known duration of the disease was about two years. In a few patients, the disease had apparently existed for only one or two months, and in one case it must have been present over ten years. Four patients were examined while definitely acidotic, four patients had a known history or had been suffering from cholecystitis or jaundice. Exophthalmic goiter was present in two patients, one of whom was suffering severely when examined. Two patients were suffering extremely from nephritis and two from pulmonary tuberculosis.

OBSERVATIONS

Examination of the table reveals that some patients showed normal enzymatic activity of the duodenal return while others showed only a trace of the activity, so that it seemed illogical to compute an average. Of the twenty-one cases in which thirty-three estimations were made, fourteen cases (67 per cent) showed proteolytic efficiency (a three hours' collection), seven cases (33 per cent) amylolytic efficiency, and twelve cases (57 per cent) lipolytic efficiency values below our minimal normal limits. In six cases (29 per cent), the efficiency of the three enzymes was within normal limits, in five cases (24 per cent), all enzymes were abnormally low. From the enzymatic activity, we found the proteolytic activity in nine cases (43 per cent), the amylolytic activity in four cases (20 per cent) and the lipolytic activity in nine cases (43 per cent) to be below our minimal normal limits. In ten cases (48 per cent), the activity of the three enzymes was within normal limits, and in three cases (14 per cent), abnormally low. The percentage of abnormalities for the total efficiency is somewhat higher than that for the enzymatic activity, owing to the fact that the amount of the duodenal return was distinctly low in several cases. Some cases showed abnormally low enzymatic activity with a normal amount of duodenal return, some showed normal enzymatic activity with a scanty amount, and others showed abnormally low enzymatic activity as well as an abnormally low duodenal return. The average amount of the duodenal return (when estimated several times for the same case, the average of the case was used for the calculation of the general average) was 87 cc (71 per cent of the normal average). The average amount of the bile pigment in three hours was 12.2 mg, which is slightly lower than

the normal average (14.9 mg), while the concentration of that is a little higher (14 mg per cent, while the normal average was 12.1 mg per cent). We could not detect any abnormalities in the pigment, though a slight difference from the normal in average was perceived. The abnormality of the enzymatic activity does not seem to exhibit any direct proportion to the severity of the impairment of the metabolism of sugar, duration of the disease, kind of diet, calories taken on previous days and acidosis. The nature of the involvement seems to be the most essential factor. The noticeable fact is that patients over 59 years of age (five cases) showed all abnormalities of the enzymatic efficiency for one or more of the enzymes. Perhaps these abnormalities in persons past middle life are due to some serious damage to both the insular and the acinous cells as the result of pancreatic fibrosis and cellular degeneration or sclerosis. The most instructive cases are cases 6 and 10 and probably the case of pancreatic cancer without glycosuria. Somewhat detailed reports of these three cases are given as representative of cases of pancreatic involvement.

REPORT OF CASES

CASE 6—Y. S., a farmer, aged 43, was admitted to the hospital on Oct. 29, 1926, complaining of jaundice, glycosuria and emaciation. There was nothing of special importance in the family history. So far as was known, he had not had measles, the patient had been vaccinated several times. He had had typhoid fever at the age of 7, which cleared up in a month. He had married at the age of 20. A syphilitic condition of the left eye occurred when he was 26, it had healed in three weeks, leaving some weakness of vision and central scotoma. He said that he had not had venereal disease, but the Wassermann reaction was strongly positive. He drank wine only occasionally, and used tobacco moderately.

Since November, 1925, he had complained of fatigue and loss of appetite, later, he was emaciated. Since January, 1926, he had also complained of thirst and hunger, and polyphagia, polydipsia and polyuria were manifested. He thought that he must have diabetes mellitus, judging from the description of the condition in the newspapers. He visited a hospital, and found that his diagnosis was correct. Since April 20, antidiabetic treatment had been given, but after that he complained of lack of appetite, nausea, and pyrosis. On May 20, he was admitted to the hospital, he was placed on a restricted diet, and insulin was administered. Following this treatment, the urine became free from sugar. Diarrhea did not occur. Since October 1, he had noticed that the urine was brown. On October 3, a physician diagnosed the condition as jaundice which continued to grow worse until October 15 to 16, after which it gradually became better. On October 29, he had visited the dispensary of the hospital, and had been admitted to the hospital.

He was well built, but showed signs of slight emaciation. The skin was somewhat pale, with a moderate degree of jaundice, and the amount of subcutaneous fatty tissue was reduced. According to the method of Meulengracht, the degree of the jaundice was 68 times positive. The pupillary reflexes were normal. Some of the teeth were missing or were carious. The tonsils were in good condition. The pulse rate was 60, and there was no fever. Abnormalities of the head, neck and extremities were not detected. The apexes were somewhat dull, otherwise the lungs were intact. The size of the heart was normal, the first sound at the apex was impure and the second pulmonic sound was accentuated. The abdomen

was increased in its transverse diameter and was distended in the epigastric region. The right lobe of the liver was palpable one and a half fingerbreadths under the arch of the right rib in the right nipple line. The border was rather hard. The surface was slippery and did not show any tenderness. The left lobe was palpable two fingerbreadths under the ensiform. The consistency of both lobes was not so hard as in cancer. The gallbladder was palpable two fingerbreadths under the arch of the right rib and was somewhat smaller than a fist. It was soft and elastic. The spleen was just palpable. The pancreas was palpable in the mid-line between the ensiform and the umbilicus, about 3 cm in breadth, some tenderness was felt and the consistency was somewhat increased. Ascites was not noted. The stomach when swollen by effervescent powder extended from the middle of the ensiform and umbilicus to the umbilical line, the right border extending three fingerbreadths right of the middle line. Roentgen-ray examination did not show any abnormality of the stomach. The free hydrochloric acid of the contents of the stomach one hour after an Ewald-Boas test meal was 34 and the total acidity 64. The sugar tolerance was not exceeded until more than 60 Gm of boiled rice had been ingested. When 100 Gm of boiled rice was ingested the blood sugar rose to 0.306 per cent and the urinary sugar to 1.2 per cent. The threshold of sugar tolerance was 0.2 per cent. The duodenal contents were examined ten times and were almost always greenish, culture showed *Staphylococcus albus*. The enzymatic activity of the duodenal contents was extremely reduced. When our three hours' test method was used, the tryptic efficiency showed from 0.28 to 1.2 kilo-units, the amylolytic efficiency from 1.1 to 13.6 kilo-units and the lipolytic efficiency from 1.7 to 6.2 kilo-units. The degree of the enzymatic activity was 0 to 20, 0 to 146 and 3 to 596 units, respectively. Hypodermic injection of 10 units of insulin (Toronto) caused marked hypoglycemia, but there was scarcely any increase in the external secretion. The feces were voluminous, when the patient was admitted they were porcelain-colored, but later they became somewhat greenish. Microscopically, a moderate amount of striated muscle fibers and steatorrhea were perceived during the whole course of the disease. The Kashiwado test gave a positive result, the Wassermann reaction was strongly positive. When the patient was admitted, a slight anemia existed, which later improved decidedly. The amylolytic activity of the blood serum, according to the method of Wohlgemuth, was 8 degrees and that of urine was 32 degrees, i. e., there was no increase of the amylolytic activity of the blood serum and urine. The jaundice lessened and disappeared in a month. The liver gradually became smaller, after from fifteen to sixteen days, the left lobe was no longer palpable, while after twenty days the gallbladder also was not palpable, only the right lobe being barely felt under the arch of the right rib. The pancreas was barely palpable after two months. Intensive treatment with Meltzer-Lyon's duodenal drainage and applications of mercurial ointment and iodide was tried, when the patient was discharged on Jan 27, 1927, the Wassermann reaction was still positive and the enzymatic activity was even less than when an examination was made on July 29, 1927, nine months after admission. The insulin treatment (35 units per day for eleven days) did not cause the diabetes to improve nor the enzymatic activity of the duodenal return to increase. Loewi's pupillar test was often tried, with negative results.

From the symptoms in this case, it is evident that it belongs to the type of so-called pancreatic diabetes. In view of the fact that the duodenal return was always greenish and contained *Staphylococcus albus*, it seems likely, at first glance, that the pancreatic involvement was caused

by contamination from the bile and pancreatic ducts. But diabetes existed long before the biliary tract disease and did not improve when the latter condition disappeared. It seems probable that syphilis had some special relation to pancreatic involvement, though it was not definitely proved.

CASE 10—S. K., a functionary, aged 49, was admitted to the hospital on April 10, 1927, complaining of thirst, cough during the night, fatigue and lack of appetite. The family history showed that the elder sister died of cholecystitis and peritonitis and the elder brother of beriberi. The patient had had smallpox when 7 years of age, measles when 11, ascariasis from 10 to 13, malaria when 13, gonorrheic gonitis when 21 and typhoid fever when 31 or 32. He said that he had not had syphilis, but two years before admission he had suffered from an eye disease, and the Wassermann reaction was strongly positive. He was given ten injections of arsphenamine, and the condition improved. He took wine moderately and tobacco excessively, he also liked sweets. He had broken the left clavicle when he was 43 years old.

In March, 1919, he had complained of thirst, a physician had examined the urine and had diagnosed the condition as diabetes mellitus. For about three years he had been fed on a restricted diet. When rice had been eliminated from his diet, he had become emaciated and weary, but he had recovered when rice was again added to the diet. In 1921, he had been advised to take care of himself as his lungs were diseased. Since February 12 or 13, 1927, he had suffered from pulmonary tuberculosis and had been confined to bed. He coughed and expectorated sputum sometimes tinged with blood almost constantly. He was feverish from the beginning and at times his temperature was as high as 39 C (102.2 F). Sweating at night was especially noticeable when he took a drug. He complained of almost continuous headache, light sleep and constipation.

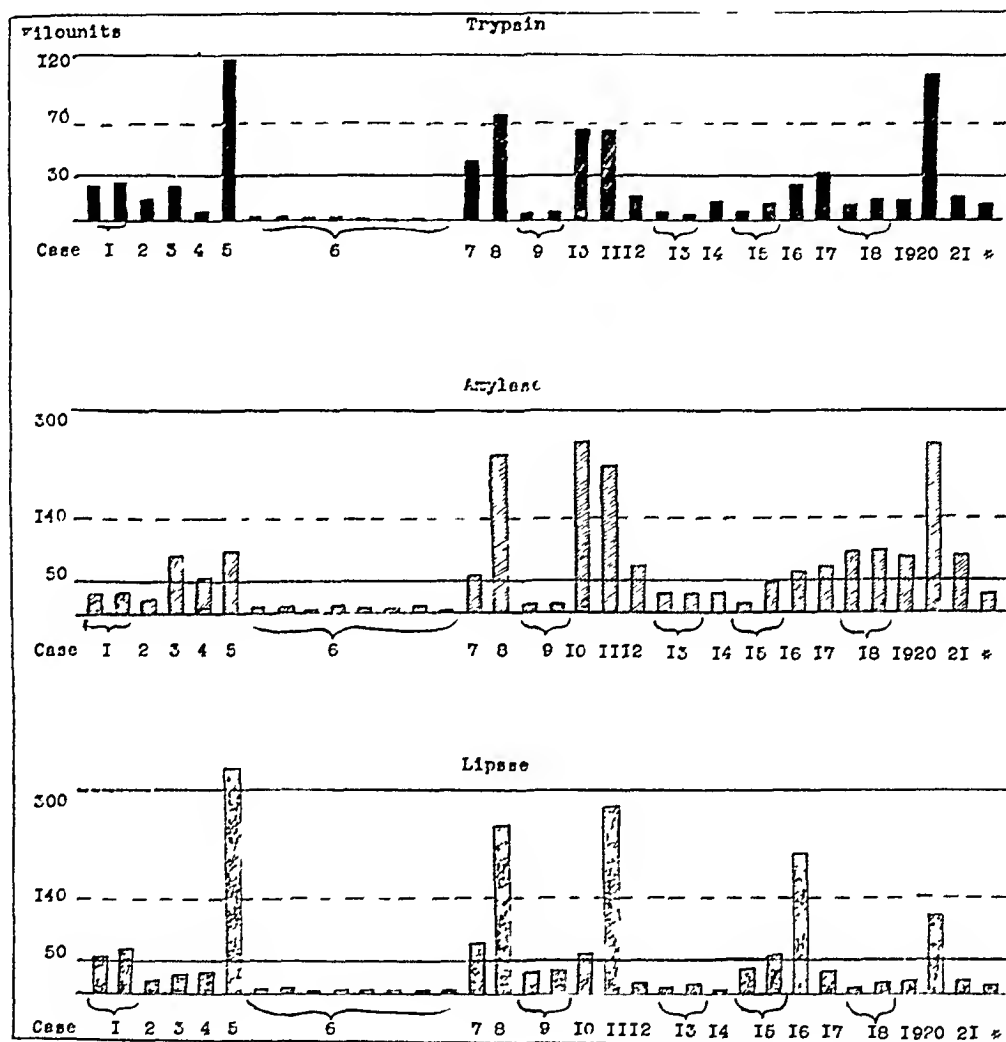
Examination showed a man of rather small stature, somewhat weakly built and with an extremely reduced amount of subcutaneous fatty tissue. The muscles were considerably relaxed. The skin was hot and normally humid. The facies was somewhat dull, the complexion was normal. The pulse rate was 90, and the beat was faint and regular. The arterial wall was rather hard. Respiration was costal abdominal. The tendon and skin reflexes were normal. The tongue was wet, but not furred and the pharynx was somewhat injected. The chest was symmetrical and the supraclavicular and infraclavicular regions were depressed. The heart was normal except for a slight accentuation of the second pulmonic sound. The dulness of the right lung extended from the apex to the first rib and in the left lung, to the second rib. In the back, the dulness extended from the apex of the right lung to the second rib and to the fourth rib on the left side. Respiratory sounds were weak and on the left side, anteriorly and posteriorly, many small and medium sized râles were audible. The extremities did not show any abnormalities except marked weakness. The sputum was slimy and mixed with blood. Elastic fibers were detected and according to Gaffky's scale, no 5 or 6 tubercle bacilli were found. The urine was yellowish brown, somewhat turbid and acid, there was a trace of protein, 4 per cent of sugar and no acetone bodies. The blood count showed 4,740,000 red blood cells, 82 per cent hemoglobin and 7,100 leukocytes, of which 70.5 per cent were polymorphonuclear neutrophils, 24 per cent, lymphocytes, and 5.5 per cent, mononuclears and transitory cells. The Wassermann reaction was weakly positive. The blood sugar rose to 0.315 per hundred cubic centimeters when 50 Gm of bread and 200 cc of milk were ingested. The fever continued almost two months with fluctuations, on April 13, 1927, when

the duodenal return was examined, it showed 37.6 C (99.7 F) in the morning and 39.2 C (102.6 F) in the afternoon. The tryptic efficiency of a three hours' collection was 67.7 kilo-units, the amylolytic 253 kilo-units and the lipolytic, 58.3 kilo-units, i. e., normal values. Intensive treatment with insulin was tried, but, owing to the progress of the pulmonary tuberculosis, the patient died on May 7. At autopsy, the pancreas did not show much alteration, it weighed 85 Gm., and the consistency was somewhat increased, there was no atrophy. Microscopically, the connective tissue was increased to some extent, but it did not show any typical fibrosis. On the other hand, the islands of Langerhans had almost completely disappeared except at the tail of the pancreas where a few remnants were detectable. The observations that the acinar tissue was almost intact and the insular tissue was extremely atrophied coincide with the clinical observations of a normal external secretion and a highly disturbed regulation of metabolism of sugar.

PANCREATIC CANCER.—T. O., a functionary, aged 45, was admitted to the hospital, Nov. 10, 1926, complaining of constipation and pain in the left hypochondriac region. The family history showed that the maternal grandmother died of apoplexy, the mother of pulmonary tuberculosis and the brothers of tuberculosis or heart disease. The patient had had measles when he was a small child, and had been vaccinated many times. He had had beriberi when 14, pyrosis when 20 and gonorrhea when 21. He said that he had never had syphilis. He smoked tobacco and liked sweets, but did not take much wine. Since he was over 10 years of age, he had suffered from constipation, a bowel movement occurring only every three or four days. On Aug. 25, 1927, as he had not had a bowel movement for four or five days he took castor oil, without effect, on the next day, he tried some powdered remedy, which caused nausea, vomiting and a movement. The following day he complained of pain in the hypochondriac region, which was not influenced by eating a meal. After several days, a similar pain occurred, and continued, there were fluctuations in intensity, but it was not colicky, and a bowel movement did not relieve the pain. In September, he was treated by a physician, and bowel movements occurred oftener. On October 6, after indigestion, he complained of severe pain in the left hypochondriac region, without vomiting. Since medicinal treatment did not relieve him, he was admitted to the hospital.

The patient was well nourished, vigorous and of medium height. The amount of subcutaneous fatty tissue was reduced. The pulse rate was 69, regular and moderately resistant to pressure. The systolic blood pressure was 129 mm. of mercury and the diastolic 74. The respiration was costal, abdominal and regular. The skin did not show any abnormalities. The lymph glands were not palpable. The facial expression was natural. Sensibility and motility were normal, as were the pupillary reflexes. The lips showed nothing of particular importance, the tongue was slightly furred and wet. The pharynx and tonsils did not show any change. The lungs and heart were normal. The abdomen showed normal swelling. There was no venous congestion, pigment anomalies or edema. The region directly on the left side of the umbilicus and the left hypochondriac region were tender. The border of the stomach was one fingerbreadth under the ensiform and two fingerbreadths above the umbilicus and right parasternal line. The liver was not palpable. The pancreas was palpable four fingerbreadths over the umbilicus and was somewhat tender. The right kidney was barely palpable. The cecum, appendix, ascending, transversal, descending and sigmoid colons were palpable. The left side showed more or less tenderness. The extremities were normal in general. The tendon reflexes were exaggerated. The urine was yellowish, clear and alkaline with a specific gravity of 1.007 and it did not contain protein, sugar,

acetone bodies, bilirubin or urobilin. There was a trace of urobilinogen and indican. The sediment did not show any abnormalities. Parasites' eggs were not detected in feces. The Weber blood test of the feces was negative, but the Adler and Boas tests were weakly positive. The stomach contents were collected fractionally after a test breakfast and were found to be normal (free hydrochloric acid 45 and total acidity 66 one hour after the test breakfast). The duodenal contents were examined on Nov 19, 1926, and the total tryptic efficiency was 10.9 kilo-units, amylolytic, 26.4 kilo-units, and lipolytic, 10.5 kilo-units, i. e., the efficiency of the three enzymes was diminished. The highest activity of trypsin



Enzymatic efficiency of the duodenal return in diabetes mellitus. The star indicates cancer of the pancreas.

was 320 units, of amylase 931 and of lipase 400, i. e., there was a decrease in the tryptic and lipolytic activity. The blood count showed 4,576,000 red blood cells, 68 per cent hemoglobin and 7,600 leukocytes, of which 61.6 per cent were polymorphonuclear neutrophils, 32.4 per cent lymphocytes and 6 per cent mononuclears. Roentgen-ray examination of the intestine showed an enormous accumulation of gas in the left flexure and descending colon. The pain in the left hypochondriac region was attributed to this distention by gas, so that the patient was treated intensively for constipation, but without effect. Moreover, we could feel a tumor

Case, Name, Sex, Age	Date	Stimulants Introduced Into the Duodenum†	Amount of Duodenal Return in 3 Hours, Cc	Degree of Enzymatic Activity†									Trypsin in 3 Hours, Kilo Unit	Amylase in 3 Hours, Kilo Unit	Lipase in 3 Hours, Kilo Unit
				Trypsin			Amylase			Lipase					
				1 Hour Unit	2 Hour Unit	3 Hour Unit	1 Hour Unit	2 Hour Unit	3 Hour Unit	1 Hour Unit	2 Hour Unit	3 Hour Unit			
1 I N ♂, 42	10/27/26	Alcohol	42 8	500 500	500	500	347	1047	1393	1953 1029	1017	775	23 2	27 6	53 6
	11/ 3/26	Alcohol	57 7	500 200	500 500	100 50	510	438	308	1250 426	624 1150	300 100	27 1	27 4	64 4
2 R K ♀, 28	10/28/26	Alcohol	46 0	320 500	800	1250	300	525	621	423 560	860	1250	15 0	19 9	19 1
3 T S ♂, 30	11/27/26	Alcohol	77 0	320 320	500 320	320 200	928 1562	1702 1257	778 804	390 190	295 222	430 380	24 5	82 8	26 8
4 B M ♂, 68	11/27/26	Alcohol	23 2	50 320	500 200	800	2418 2404	1774 1310	1842	120 350	1425 940	5300	6 7	53 9	29 8
5 K K ♂, 44	12/21/26	Alcohol	92 5	1250 800	1250 800	2000	1064 694	1094 795	1432	4050 2650	1390 596	5900	110 8	91 4	327 9
6 Y S ♂, 43	11/13/26	Alcohol	101 0	0 5	5 5	5	51 59	64 13	146 73	70 596	872 228	280 340	0 42	8 6	3 5
	11/24/26	25% mag- nesium sul- phate, 50 cc	111 5	0 8	20 20	0 0	0 29	0 42	47 45	3 20	135 150	100 180	0 69	2 0	6 2
	11/26/26	Ether, 2 cc	101 5	5 5	5 20	5	18 34	1 23	6	10 19	11 17	17	0 46	2 3	1 7
	12/10/26	Alcohol	156 0	16 10	5 5	0 2 5	59 82	90 84	121 125	25 23	22 21	14 19	1 24	13 6	3 5
	12/15/26	Alcohol, insulin, 10 units hypodermi- cally	141 5	0 5	0 5	—	120 64	61 31	—	17 23	19 25	—	0 50	7 9	3 2
	1/16/27	Alcohol	109 5	0	5	5	23 60	39	71	27 10	13	25	0 88	6 5	2 7
	1/25/27	0.2% hy- drochloric acid, 30 cc	176 5	5	0	5	59	104	58	23	12	18	0 81	11 0	3 7
7 K K ♂, 34	7/29/27	No	96 0	10	0	0	15	4	11	8	4	3	0 28	1 1	
8 S S ♂, 44	1/ 8/27	Alcohol	118 5	200 200	500 500	500	408 1025	1027 558	746	238 220	780 570	1904 632	42 2	58 2	75 6
9 K S ♂, 72	2/ 8/27	Water	159 0	500	500	500	1706	1085	1663	1125	1690	1590	79 5	233 4	245 3
	3/18/27	No	36 0	100 0	100 320	200	379 92	634 611	249	280 408	1260 2024	588	4 9	12 8	26 4
	3/20/27	Insulin, 10 units hy- podermi- cally	59 0	0 0	100 320	320	175	454	295	—	145	435	7 4	16 7	31 8
10 S K ♂, 49	4/13/27	Water	122 0	320	500	800	2083	2029	2101	104	210	984	67 7	253 3	58 2
11 K S ♂, 36	4/20/27	Water	154 5	500	500	500	1353	1675	1353	1204	1357	2544	66 6	218 7	278 0
12 Y T ♀, 60	5/31/27	No	59 5	320	320	320	1091	1207	1030	139	230	330	18 9	68 2	12 6
13 S Y ♂, 35	6/ 1/27	Water	80 0	60	60	80	431	384	255	138	48	60	5 4	28 4	6 7
	6/17/27	Water	76 0	50	40	60	377	298	377	258	100	85	3 8	26 6	* 10 8
14 K K ♂, 69	6/10/27	Water	70 5	10	320	200	208	439	551	66	25	14	13 6	29 4	2 3
15 S O ♀, 44	6/15/27	No	55 6	10	200	10	43	373	423	284	960	320	6 1	17 0	34 9
16 S N ♀, 31	7/ 2/27	No	42 3	160	160	400	867	1360	990	804	915	1806	12 1	43 7	56 4
	6/19/27	No	66 0	200 500	200 0	0	554 936	395 56	113	1640 1190	546 310	200 2400	24 1	60 3	202 1
17 T D ♂, 26	6/22/27	No	70 5	200	500	500	510	900	1084	140	200	480	32 2	68 6	27 3
18 R S ♂, 59	9/ 9/27	Water	85 0	100	50	250	1054	854	1405	32	54	198	10 7	93 0	6 6
19 L I ♂, 42	9/30/27	Water	74 9	100	0	250	768	592	1382	148	87	140	15 9	95 9	16 6
	9/23/27	Water	102 0	100	250	160	402	2187	930	115	100	465	15 2	93 0	18 0
20 K I ♂, 46	9/27/27	Water	106 0	500	1250	1250	2273	2313	2442	468	1130	1550	107 0	249 9	117 0
21 M S ♀, 45	11/ 4/27	Water	63 0	200	0	320	1290	890	1538	275	85	400	14 1	84 3	18 9
† T O ♂, 45	11/19/26	Alcohol	34 5	320	320	—	901	931	—	280	400	—	10 9	26 4	10 5

* In this table, ♂ indicates male, ♀, female

† Cancer of the pancreas

‡ The cases, in which two degrees of enzymatic activity are shown, mean that every half hour collections were estimated separately

§ Alcohol, 10% solution, 30 cc, water, 30 cc

Bile Pigment in 3 Hours, Mg	Fasting Blood Sugar, per Cent	Highest Blood Sugar During the Course, per Cent	Urinary Sugar, per Cent	Highest Urinary Sugar During the Course, per Cent	Diabetic Acid#	Severity of the Disease	Duration in Years	Weight in Kg	Diet§	Boiled Rice, Gm	Calories per Kg	Comment
32	0.100	0.521	—	8.0	+	Severe	1	48.5	Restricted	0	33.0	
58												
13	0.160	0.263	—	7.9	—	Severe	1	36.0	Restricted	90	35.5	
42	0.114	0.204	—	7.7	(++)	Severe	1	51.7	Restricted	240	37.3	
04	0.100	0.440	—	6.3	(+++)	Severe	11	53.8	Restricted	150	20.0	
15.9	0.164	0.381	2.0	5.6	—	Severe	5	41.0	Free	Plenty		+ Retinitis diabetica, nephritis, neuralgia
92	0.150	0.306	—	2.0	(++)	Severe	1	58.2	Restricted	180	38.0	+ Cholecystitis
61			—		—				Restricted	180	38.0	
69			—		—				Restricted	180	38.0	
132			0.6		—				Restricted	180	38.0	
136	0.141		—		—				Restricted	250	40.0	
131					—				Restricted	250	40.0	
64					—			61.5	Restricted	250	40.0	
21	0.227		—		—				Restricted	250	40.0	
11.5		0.195	3.1	3.9	(+++)	Severe	0.5	49.1	Free	Plenty		
93	0.265	0.561	5.0	9.8	—	Severe	0.3	46.6	Free	Plenty	Ca 35.0	+ Jaundice
60	0.227	0.510	4.1	8.5	—	Severe	0.8	43.5	Free	Plenty	32.0	
11.5					—							
11.5	0.106	0.315	2.5	6.7	—	Severe	8		Free		20.0	+ Pulmonary tuberculosis
18.3	0.104	0.193	—	10.5	—	Mild	1	54.7	Restricted	480	31.8	
68	0.150	0.415	—	5.0	—	Severe	2	30.4	Restricted	240	19.0	Catarrhal jaundice in 12 years, + pulmonary tuberculosis, exophthalmic goiter
13	0.110	0.220	—	4.6	—	Mild	Ca 3	47.5	Free	Plenty		+ Exophthalmic goiter, periodical paralysis
02					—							
7.9	0.202	0.534	—	7.7	+	Severe	0.5	38.7	Restricted	60	38.0	
05	0.123	0.191	—	4.8	—	Mediocre	0.2	41.1	Restricted	200	40.5	+ Essential thrombopenia
35					—			41.0	Restricted	470	45.8	
19.9	0.311	0.498	9.9	13.0	—	Severe	1	27.5	Free	810	51.9	
18.7	0.315	0.440	6.5	9.7	(+++)	Severe	2	35.1	Free	780	Ca 35.7	
96	0.180				(+++)							
14.8					—	Mild		44.4	Free	Plenty	Ca 20.0	+ Nephrocirrhosis, arteriosclerosis
4.8	0.097	0.225	—	1.9	—	Mild	1	53.8	Restricted	600	41.3	
41.2	0.085	0.202	—	0.4	—	Mild	0.5	42.7	Restricted	900	35.4	Cholelithiasis 26 yrs
13.6	0.134	0.293	—	5.7	—	Mediocre	5	49.5	Free	Plenty	Ca 28.0	+ Pulmonary tuberculosis
28					—							

The marks in the brackets show that the diabetic acid reaction became positive sometime during the course of observation.

§ Restricted diet, in addition to rice, consisted of foods poor in carbohydrates such as eggs, beef, calf, fowl, fish, butter, cabbage, spinach, milk, tofu, tofukara and aburagō so that the amount of the rice may be seen as the measure of carbohydrate permitted.

under the arch of the left rib inside of the nipple line, so that we decided to try an exploratory laparotomy. On December 1, operation was performed by Professor Shioda, who found a cancer the size of a goose egg at the tail of the pancreas.

In this case, there was a disturbance of the external secretion of the pancreas, while the internal secretion was normal.

The foregoing cases show a representative disturbance of the pancreatic function. In the first case (case 6), there was a severe disturbance of both the internal and the external secretion, which showed that there was general involvement of the pancreas. In the second case (case 10), there was a severe disturbance of the internal secretion while the external secretion was normal, and the autopsy proved that the acinar cells remained almost intact while the insular cells were extremely atrophied. In the third case (cancer of the pancreas), the internal secretion was still sufficient to maintain the normal regulation of metabolism of sugar, while the external secretion was greatly diminished. Any functional disturbance of the pancreas might be grouped with one of these three forms, between which there are numerous transitional types.

Insulin usually causes active external secretion of the pancreas, increasing both the amount and the enzymatic activity when marked hypoglycemia develops. In two cases of severe diabetes (cases 6 and 9) with severe disturbance of the external secretion, we found almost no increase in one case, and only a slight increase in another case. Perhaps the structural alterations had already progressed so far that the cells which were still active were too few to react to stimulation.

COMMENT

In view of the foregoing observations, it is interesting to discuss the significance of the results obtained by our three hour method of calculating the total enzymatic efficiency. As already noted, more than one half of the cases (about 70 per cent) showed a diminution in the total efficiency of one or more of the pancreatic enzymes, the percentage of abnormality of the enzymatic activity was somewhat less (about one-half). The deviation of abnormalities in these two standards depends mainly on the fact that the duodenal return was small in some cases. It is possible that in some cases the enzymatic activity may be high when the secretion is scanty. This has been proved by our three hour method. The disturbance in the pancreatic function is manifest by diminution either of the enzymatic activity or of the amount of pancreatic juice, or of both. The method in which only the enzymatic activity is used to determine the efficiency of the pancreatic function does not include the two latter factors. On the other hand, it is also possible for a profuse secretion of the pancreas to be diluted by saliva, gastric juice and biliary secretion so that the enzymatic activity is relatively low. Jones, Castle,

Mulholland and Bailey noted the striking fact that the amylolytic activity was apparently diminished in only 9 per cent of the cases, whereas the proteolytic activity and the lipolytic activity showed definite reductions below the minimum normal level in over a third of the cases. The same striking fact was confirmed in our cases, amylolytic efficiency being diminished in only one third of the cases, whereas proteolytic and lipolytic efficiency showed reductions below the minimum normal level in over one half of the cases. Just why there should be a dissociation of these ferment actions would be extremely interesting to know, at present, however, we cannot offer a reasonable explanation. At least this disturbance cannot be attributed to the improper digestion of fat and protein in diabetes mellitus. In other conditions than diabetes, we could also find the same striking feature when disturbances of the enzymatic activity occurred. It is definitely proved that amylolytic activity is usually maintained with more extraordinary tenacity than the other two ferments.

That the severity of the diabetes does not necessarily run parallel to the degree of disturbance of the external secretion has already been mentioned. Some cases showed severe disturbance of both the internal and the external secretion of the pancreas, whereas others showed marked disturbance only of the internal secretion while the external secretion remained normal. There are also diseases in which the internal secretion is sufficient to maintain the normal regulation of metabolism of sugar, whereas the external secretion is markedly disturbed. Representative cases of these three forms are described in the foregoing case reports.

It is well known that marked undernutrition, with the resulting loss of weight, is accompanied by changes in the size and function of the pancreas. The majority of the patients included in this series, however, were not extremely emaciated and previous to the examination ingested over 30 calories per kilogram of body weight per day. The lowest figures for enzymatic activity were not necessarily found in patients who were strikingly underweight. In this connection, we agree with the observations of Jones and his co-workers, who also emphasized a marked increase in the elimination of the bile pigment in diabetes mellitus. Unfortunately, as far as the elimination of bilirubin was concerned, we could not confirm these data.

Jones and his co-workers noted that 19 per cent of their patients showed the characteristic symptoms of cholelithiasis. In our twenty-one cases, we could confirm a history of jaundice in four cases (19 per cent), in two of the cases (cases 12 and 20) cholecystitis or cholelithiasis developed a long time before the diabetes occurred, in one case (case 8), cholelithiasis and diabetes were associated and in another (case 6) the cholecystitis apparently appeared during the course of the diabetes.

Considering the historical data carefully, we hesitate at present to accept the etiologic rôle of gallbladder disease in these four cases

Two patients in the series had a history of exophthalmic goiter, one patient (case 12) showed scarcely any symptoms of this disease when examined, whereas another (case 13) showed typical and severe symptoms of exophthalmic goiter, accompanied by periodic paralysis. The latter case is especially interesting. The glycosuria showed the highest percentage noted for thyrogenic glycosuria (highest urinary sugar, 4.6 per hundred cubic centimeters). It is well known that periodic paralysis is often accompanied by glycosuria and is considered by some authors (Lundborg, Shinosaki and others) as the manifestation of involvement of the parathyroid gland (hyperfunction). On the other hand, in exophthalmic goiter a special anatomic change in the pancreas, in both the acinous and the insular tissues, is noted. In this case, therefore, it seems difficult to decide whether the disturbance in the regulation sugar metabolism might be attributed to the pluriglandular involvement or to the pancreatic damage. The activity as well as the efficiency of the three pancreatic ferments, however, showed a marked decrease, so that the disturbance seemed to be due mainly to a general involvement of the pancreas associated with pluriglandular disease.

It is striking that the older patients showed almost all abnormalities of enzymatic efficiency of one or more of the enzymes. It is probable that some serious damage to both the insular and acinous cells (fibrosis and cellular degeneration or sclerosis) was the cause of the abnormalities in these cases.

SUMMARY

1. An unselected group of twenty-one diabetic patients was examined according to our newly devised method for evidence of alteration in the pancreatic activity. The total proteolytic efficiency as determined in 67 per cent of the three hour specimens showed amylolytic efficiency in 33 per cent and lipolytic efficiency in 57 per cent, values below our minimal normal limits. The efficiency of the three enzymes was within normal limits in 29 per cent of the cases, in 24 per cent the activity of all the enzymes was abnormally low. From the enzymatic activity the proteolytic activity was estimated in 43 per cent of the cases, the amylolytic activity in 20 per cent and the lipolytic activity in 43 per cent, the values were below our minimal normal limits. In 48 per cent of the cases, the activity of three enzymes proved to be within normal limits and in 14 per cent, abnormally low. The deviation of abnormalities in these two standards depends mainly on the fact that the amount of the duodenal return was scanty in some cases. The disturbance of the pancreatic function manifests itself in the diminution either of the enzymatic activity or of the amount of the pancreatic juice or of both. The method

in which only the enzymatic activity is used as a measurement of the pancreatic function does not take into consideration diminution in the secretion of the pancreatic juice or that both the pancreatic juice and the enzymatic activity may be decreased. The greatest alterations in enzymatic efficiency as well as activity were noted in the proteolytic and lipolytic ferments.

2 The severity of the diabetes is not necessarily parallel with the degree of disturbance in the external secretion. Some cases showed severe disturbance in both the internal and the external secretion of the pancreas, whereas others showed a marked disturbance only in the internal secretion, while the external secretion remained normal. There are also diseases in which the internal secretion of the pancreas is sufficient to maintain the normal regulation of metabolism of sugar, whereas the external secretion is markedly disturbed. Representative cases of these three types are described in detail.

3 Old patients showed almost all abnormalities of the enzymatic efficiency of one or more of the enzymes. It is likely that some serious damage to both the insular and acinous cells causes the abnormalities in these cases.

THE PREVENTION OF EXPERIMENTAL EXUDATES BY THE PARATHYROID HORMONE (COLLIP)*

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The view is commonly held that calcium salts inhibit the formation of effusions. The literature dealing with the experimental work on this subject seems to indicate that calcium is extremely effective for that purpose. It has not proved so in clinical practice in the manner in which the calcium salts are generally given. In a previous paper,¹ I described experiments that confirm the view that the calcium salts inhibit the formation of experimental exudates and pointed out some of the limitations that might readily vitiate the clinical usefulness of this antagonism. From that study, it appeared evident that the absolute inhibitory effect of the calcium salts is rather limited, that it depends on the dose of calcium and the intensity of the irritation, that an extremely large dose of calcium is necessary to inhibit the effects of moderate irritation, and that the effect of more intense irritation is practically uninfluenced even by fatal doses of calcium.

It was suggested that the failure to obtain more satisfactory results with the use of calcium salts in the prevention of effusions in man might be due, in part, to insufficient doses of the latter, and the difficulty of producing sufficiently persistent hypercalcemia with calcium salts. The parathyroid hormone produces hypercalcemia of considerable duration in normal animals.² A number of reports have appeared,³ which show that the parathyroid hormone produces a diuresis and loss of fluid in certain patients with edema. The present study was undertaken to determine if the parathyroid hormone will prevent the formation of experimental effusions.

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1 Gold, Harry. On the Prevention of Experimental Effusions by Calcium Salts, *J Pharmacol & Exper Therap*, to be published

2 Collip, J B. The Parathyroid Glands, *Medicine* **5** 1 (Feb) 1926

3 Davidson, J R. A Case of Adolescent Myxedema, Accompanied by Tetany of Parathyroid Origin, Treated with Collip's Parathyroid Extract, *Canad M A J* **15** 803 (Aug) 1925. Mason, E H. A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract, *ibid* **16** 538 (May) 1926. Meakins, J C. Reaction of Chronic Nephrosis to Thyroid and Parathyroid Medication, *J A M A* **89** 149 (July 9) 1927. McCann, W S. Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, *ibid* **90** 249 (Jan) 1928

EXPERIMENTAL WORK

Sixteen experiments were performed on dogs. The results are given in the accompanying table. Pleural effusions were produced by the introduction of an irritant (solution of copper sulphate) into the pleural cavity by means of a pleural cannula. About twenty-four hours later, the animal was

Effect of Parathyroid Hormone on Effusions Produced by Injection of Solution of Copper Sulphate into the Pleural Cavity

Num ber	Weight of Dog in kg	Dose in Cc	Copper Sulphate		Interval in Hours Follow- ing In- jection of Solu- tion of Copper Sulphate	Cubi- centi- meters of Fluid in Pleural Cavity	Dose of Hormone in Units	Remarks
			Per- cent- age of Solu- tion	Per- cent- age of Solu- tion				
1	5.40	1	1	1	24	2		
2	6.50	1	1	1	24	2		
3	9.30	1	1	1	20	90		
4	8.54	2	1	1	20	115		
5	8.68	2	1	1	29	150		
6	4.96	2	1	1	20	151		
7	8.30	1	1	1	22	170		
1	6.38	2	1	1	24	0	150	Hormone in 3 doses of 50 units each, first dose 5 hours before injection of solution of copper sulphate, nausea
2	9.00	1	1	1	20	0	200	Hormone in 4 doses of 50 units each, first dose 15 hours before injection of solution of copper sulphate, animal was depressed and vomited
3	8.60	1	1	1	22	0	100	Hormone in 2 doses of 50 units each, first dose 13 hours before injection of solution of copper sulphate, vomiting, diarrhea, serum calcium, 165 mg, animal appeared normal the following morning
4	6.60	1	1	1	24	0	50	Hormone in 1 dose 10 hours before injection of solution of copper sulphate, slight depression, serum calcium, 194 mg, appeared normal the following morning
5	4.82	1	1	1	24	25	150	Hormone in 3 doses of 50 units each, first dose 5 hours before injection of solution of copper sulphate, animal normal
6	10.94	2	1	1	20	26	150	Hormone in 2 doses, first 100 units 15 hours before injection of solution of copper sulphate, vomited other wise normal, pneumonia after injection of solution of copper sulphate, serum calcium, 18 mg
7	5.72	2	1	1	20	30	200	Hormone in 3 doses of 100, 50 and 50 units, first 100 units 14 hours before injection of solution of copper sulphate, vomited, animal normal the following morning
8	3.50	1	1	1	44	44	50	Hormone in 1 dose 4 hours before injection of solution of copper sulphate, animal normal
9	7.30	2	1	1	21	110	100	Hormone in 2 doses of 50 units each, first dose 14 hours before injection of solution of copper sulphate, normal, serum calcium, 125 mg

anesthetized, the chest was opened and the pleural fluid was removed and measured. Seven animals were used for control experiments. In these, there was scarcely any external evidence of disturbance, even when the pleural cavity contained as much as 170 cc of exudate. The remaining nine dogs received the parathyroid hormone prior to the injection of the irritant. The hormone was generally given subcutaneously in several doses at intervals of about

two to four hours, the first dose being administered from four to fifteen hours preceding the injection of the copper sulphate solution into the pleural cavity. Some animals showed evidence of the toxic effects of the hormone, such as nausea, vomiting, diarrhea and depression, the others appeared quite normal. At the time of the intrapleural injection, the blood calcium was determined in four cases. By the method of Clark and Collip,⁴ the serum calcium was found to range from 12.5 to 19.4 mg per hundred cubic centimeters of blood.

COMMENT

The results, as seen in the table, indicate that the parathyroid hormone (Collip), given subcutaneously, diminishes or prevents pleural effusions following the intrapleural injection of an irritant (solution of copper sulphate). In the dog, it appears that considerable hypercalcemia is necessary, because the animal (number 9) that had a relatively low serum calcium behaved practically the same as the normal control animal in response to the irritation.

The observation that certain doses of the parathyroid hormone inhibit experimental exudates produced by a given kind and degree of irritation has interesting clinical possibilities. To what extent it will prove applicable for the prevention of clinical effusions remains to be determined by direct observations. Its usefulness will almost certainly be limited by such factors as the cause of the effusion, the intensity of the irritation, the degree to which the hormone will produce hypercalcemia in man without toxic symptoms and the degree of hypercalcemia necessary in man to impair the passage of fluid from the circulation into the tissues or body cavities.

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⁴ Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63** 461 (March) 1925.

CONTINUED ADMINISTRATION OF IODIDE AND OTHER SALTS

COMPARATIVE EFFECTS ON WEIGHT AND GROWTH OF THE BODY *

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The objections that have been raised against the prolonged administration of iodide in small doses are conspicuously unsupported by trustworthy evidence. The alleged deleterious effects are not clearly defined. The disturbing effects sometimes attributed to the use of iodide or iodine in the treatment for abnormalities of the thyroid may be due to the disease and not to the iodide. With the exception of the well known changes in the thyroid gland during hyperplasia and in cases of simple goiter and certain changes in the metabolism, important alterations in other organs and functions as a result of small doses of iodide have not been demonstrated. Marine's ¹ statistical studies of clinical data indicate the lack of evidence of the alleged deleterious effects of iodide, and recently Read, Walker and McKenney ² failed to demonstrate any effects on the pulse rate in human subjects observed during relatively short periods. Clinical data, however, could not reflect more than acute or periodic effects. A more critical test would be administration to animals over long periods under controlled conditions.

Changes in weight and growth of the body reflect the sum total of effects on functions of the body, so that objective evidence of this character would be important with reference to the iodide action under discussion. Although the results of such studies may not always be easy to interpret, yet if they are definite, they are suggestive, at least, and offer a point of departure for further study of specialized functions. Studies of the action of iodide over long periods along these lines have not been made previously. Clinically, they would be impracticable, but experimentally they are feasible with small animals. During the past four years, we have carried on such studies on rats and have observed the effects of iodide and other salts during from about one

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¹ Marine Medicine 6 127, 1927

² Read, Walker and McKenney Proc Soc Exper Biol & Med 24 322, 1927

seventh to seven twelfths of the life span of these animals. The results obtained are interesting and sufficiently conclusive to warrant a report. The effects of the other salts were found to be in marked contrast to those of the iodide, thus emphasizing the distinctiveness of iodide, which was found to be beneficial and at least not harmful. Our results corroborate and correlate with interesting and important results from small doses of iodide reported in the literature of veterinary medicine.

METHOD

Four experiments were made with rats on a complete diet, one yearly during four successive years, from 1925 to 1928 inclusive, and one experiment with rats on a deficient diet. This provided ample opportunity for testing the validity of the results on different strains of rats, during different seasons, and for extending the comparisons to other salts. Only males were used, the groups for each experiment being from the same litter as much as possible. The number of animals in the different experiments ranged from three to five in a group for each salt and control, this is indicated in the accompanying charts. The groups on medicated food were always accompanied by control groups on untreated food. All experiments were started with young animals of equal weight (about 40 Gm). The animals were weighed twice weekly throughout the experiments. The diet used was the modified adequate or complete diet of Osborne and Mendel, as used by Dr. Thomas Addis of the department of medicine,³ 1 Kg of which contained cornstarch, 440 Gm, casein, 160 Gm, lard, 140 Gm, yeast, 100 Gm, ground alfalfa, 20 Gm, cod liver oil, 109 cc, and the salt mixture of Osborne and Mendel,⁴ 40 Gm, this salt mixture contains about 0.0032 per cent of potassium iodide. The medicated foods were prepared by first dissolving the salt in a suitable small volume of water and then incorporating it with the food. The foods were dispensed in tared porcelain cups, water was provided liberally. The concentrations and doses of the salts varied.

Sodium iodide (dry) was used in a concentration of 0.01 per cent, which corresponded to about 1 mg daily per rat or about 3.3 mg daily per kilogram throughout the major part of the life of the rats. This dosage of iodide would correspond to about 0.23 Gm (3½ grains) daily for an adult of 70 Kg and might represent the daily amount used during a course of medication with iodide for the prevention of simple goiter, and that used in the treatment of toxic goiter and for chronic inflammations such as bronchitis, asthma and arthritis, but would be several times greater than the daily dose of iodide used in the form of iodized table salt.

The equivalent concentration of sodium sulphocyanate was 0.007 per cent, and of sodium bromide, 0.0054 per cent, the daily doses per rat of these salts being about 0.6 and 0.5 mg, respectively, and the daily doses per kilogram probably not over 2 mg of each. These doses were chosen for comparison with iodide on a chemical basis. The median daily consumption of the sulphocyanate food was about 10 per cent less than that of the iodide, and of the bromide food about 22 per cent less.

3 Dr. Addis provided generous supplies of this diet, the details of this and other diets and the methods of handling rats are given in the paper of MacKay and MacKay (*Am J Physiol* **83** 179, 1927) from his laboratory.

4 Osborne and Mendel *J Biol Chem* **37** 557, 1919.

Arsenic was used as the official Fowler's solution (liquor potassii arsenitis, U S P), the concentration in food corresponding to 0.01 per cent of arsenous oxide, the daily dose per rat was about 0.76 mg of arsenic trioxide estimated on the basis of a median consumption of 8 Gm of food daily, and the daily dose per kilogram was not more than 2.5 mg, therefore, about three-quarters the dosage of iodide and nearly the equal of the doses of sulphocyanate and bromide. This dosage would be toxic for man, being the equivalent of 175 mg or nearly 3 grains for a man weighing 70 Kg, this dosage is known from Sollmann's work⁵ to cause a definite loss of body weight in rats. The rats on arsenical food ate about 20 per cent less than those on the control and iodide foods. The dosage of manganese (as sulphate) in the experiment with the dietary for rickets was the same as that of arsenic.

Sodium borate was used in a concentration of 0.014 per cent which was ten times that necessary for plant growth found by Brenchley,⁶ the daily dosage per rat was 1.12 mg and the dose per kilogram per day about 3.7 mg, that is, nearly the same as that of iodide. This much or more would be ingested daily in preserved food. The consumption of borated food was 10 per cent less than that of iodized food, i.e., a median of 8.4 Gm per day.

Thallium acetate was used in a concentration of 0.0014 per cent, the daily dose per rat was about 0.11 mg, or about 0.45 mg per kilogram per day, the consumption of the thallium food was 16 per cent less than that of the control and iodized foods, and the animals died before maturity. This dose has been found by Buschke and Peiser⁷ to cause definite effects in rats.

The results are presented in charts 1, 2, 3, 4 and 5, each of which gives the data on body weight and food consumption of an experiment. The curves represent median values at the end of each month, although weekly records in each experiment had been made throughout the work. Weekly records, however, were too unwieldy for reproduction and did not give more information than the monthly records. It will be understood that the values relating to changes in body weight, food consumption, etc., in the text all represent medians which were derived from tabulations. Charts 1, 2, 3 and 4 represent the results of experiments with salts in complete diet, and chart 5, in a rachitic diet.

IODIDE

Collectively, the experiments made show two main results with reference to iodide, (1) an increase in weight or growth of the body sometime during the course of ingestion of the iodized food as compared with the controls on unmedicated food, (2) in contrast with this effect of the iodide and generally with the controls, a reduction in the body weight and growth after medication with all other salts. These results hold for the majority, or four, of the five experiments made.

5 Sollmann J Pharm & Exper Therap **18** 43, 1921

6 Brenchley Inorganic Plant Poisons and Stimulants, ed 2, London, Cambridge University Press, 1927

7 Buschke and Peiser Klin Wchnschr **5** 977, 1926

The increases caused by the iodide were variable, although during the course of an experiment they would be considerable for several months at a time. This can be seen from the accompanying charts. An approximate figure for all groups during the periods of observation made would be an increase of about 10 or 15 per cent. The importance of this figure lies in the facts that it represents an increase over considerable periods (months) and that the absolute increase would be important in practice during short or long periods, when transferred to man and larger organisms.

The actual values from the tabulations of our data on rats were as follows. In the majority, or three, of the four experiments made with the rats on complete diet, iodide increased the body weight from 6 to 25 per cent. An increase of 9 per cent was observed in the group of rats observed during twenty-one months (chart 1), a 6 per cent increase in the group observed during twelve months (chart 2), and an increase of 25 per cent in the group observed during five months (chart 4). The rats of each of these three groups which had received iodide ate the same amount of food as their controls on untreated food, namely, 10 Gm, 9.1 Gm, and 7 Gm, respectively. Apparently, therefore, the increases in body weight occurred independently of food consumption. Only one group of rats (chart 3) showed a loss of 7 per cent in body weight during seven months' observation, but their daily food consumption was 6 per cent less than that of their controls. This suggests that the diminished food consumption caused the difference in response to iodide from that of the majority of the rats. These rats grew less because they ate less. The diminished eating indicated some abnormality. This is not ascribed to an abnormality of the appetite due to the iodide, because the appetites of the majority of the rats showing increases in weight (positive experiments) were not affected.

Iodide in Rats on Deficient Diet—Iodide was compared with arsenic and manganese in rats on the diet of Sherman and Pappenheimer⁸ used for the production of experimental ticks, in connection with some other experiments. The results were interesting, because the iodide showed the usual difference from arsenic and also a difference from manganese. The iodide exerted a beneficial effect on growth and duration of life, while the rats receiving arsenic and manganese showed greater losses of weight and earlier deaths than the rats given iodide and the control rats. Chart 5 illustrates the course of events in these rats.

Experiments with other deficient diets were not made because of the erratic results obtained. The only agent observed to have bene-

⁸ Sherman and Pappenheimer. *Proc Soc Exper Biol & Med* **18** 193, 1921.

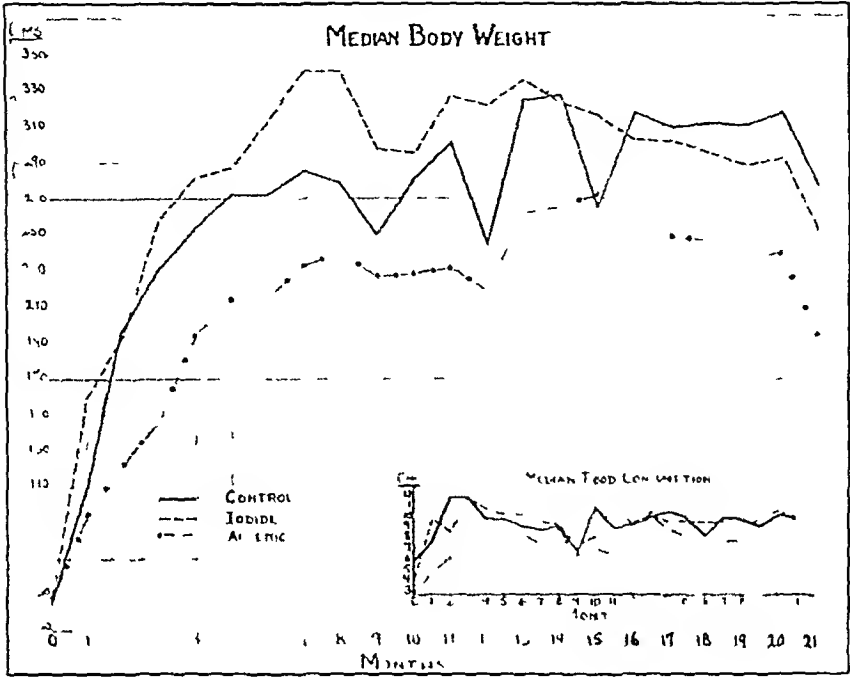


Chart 1—Iodide and arsenic in rats on complete diet, three rats to a group (experiment 1) In all the charts, control rats were on the same but unmedi-
cated diet

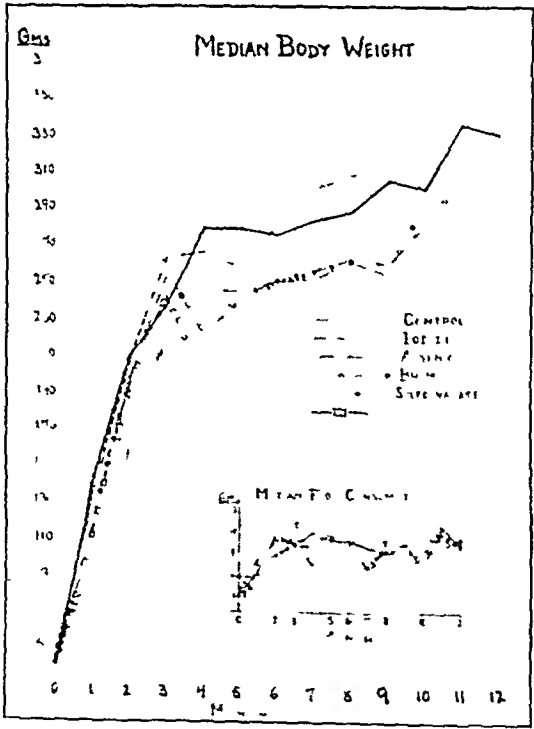


Chart 2—Iodide, arsenic, bromide, sulphocyanate and thallium in rats on complete diet, five rats to a group (experiment 2)

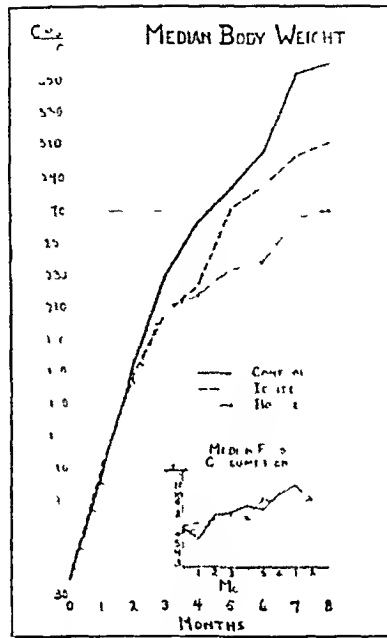


Chart 3—Iodide and borate in rats on complete diet, five rats to a group (experiment 3)

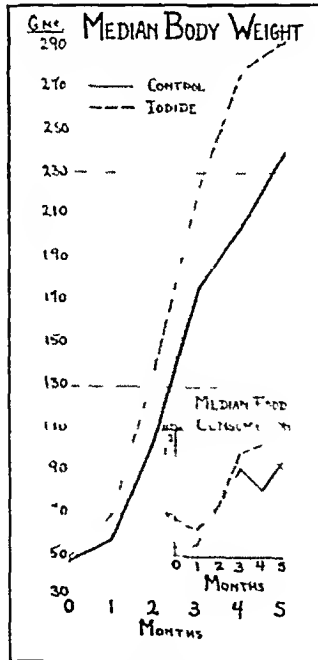


Chart 4—Iodide in rats on complete diet, four rats to a group (experiment 4)

ficial effects in rats on a growth-deficiency diet was butylamine in 0.01 per cent concentration added to the food. This amine also caused an occasional spectacular recovery when an injection of it was made into pigeons which were moribund as a result of a polyneuritic diet (polished rice). The variable mortality, the intervention of infections, etc., in animals on deficiency diets made it difficult to interpret the results. In any case the results on complete dietary are of greater importance in the present connection.

It may be concluded that iodide in continued small daily doses in food over long periods causes moderate though variable increases in body weight, and that it does not impair growth except occasionally when the food consumption may be less. In contrast with these actions

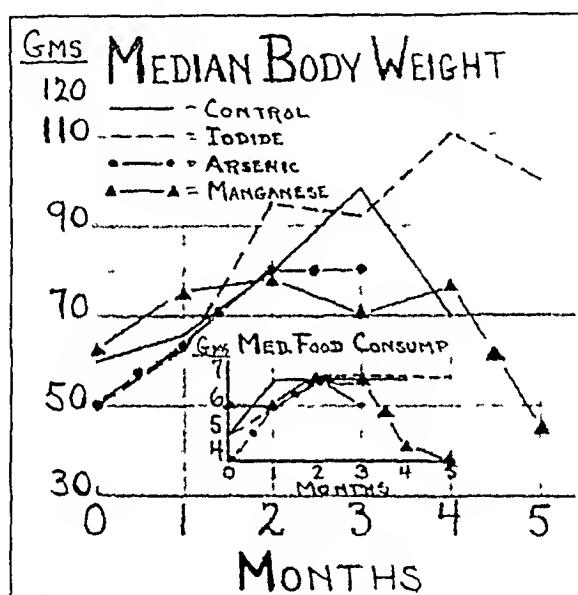


Chart 5—Iodide, arsenic and manganese in rats on rachitic dietary, three rats to a group (experiment 5). The controls were on an unmedicated rachitic diet.

of the iodide were the detrimental effects of a number of other salts, which served as further controls on the iodide since they were produced simultaneously in the different groups of rats.

OTHER SALTS

The results with the other salts were sufficiently interesting to be worthy of a separate and brief summary, according to each salt. The doses were given in the first part of the paper.

Sulphocyanate—In many respects, sulphocyanate is chemically and pharmacologically close to iodide, but the effects on body weight were the opposite, causing a reduction of 10 per cent. The daily consumption of food was also reduced 10 per cent, and this probably explains

the corresponding loss of body weight, just as in the case of the iodide in experiment 3, which has already been discussed

Arsenic—Used as the official liquor potassii arsenitis (Fowler's solution) during twenty-one months in experiment 1 and during twelve months in experiment 2, arsenic caused losses in body weight of 20 and 10 per cent, respectively, the daily food consumption was reduced about 22 per cent (experiment 1) and 10 per cent (experiment 2). Here, again, the diminished food consumption explains the retarded growth of the animals. Two of the rats in experiment 2 died at the end of four months and ten months. Our results with arsenic generally confirm those of Sollmann⁵ on chronic intoxication with arsenic trioxide, their main importance in the present connection being as controls of the general technic and response of the rats used alongside of their partners receiving iodide, thus indicating the correctness of our results with the latter.

Borate—Used as sodium borate during seven months, this salt caused a median loss of 17 per cent in body weight. The daily food consumption was reduced somewhat less, i.e., 10 per cent, but would practically account for the loss of growth. Rats of the same litter receiving iodide at the same time showed losses of only 7 per cent in body weight, and only 6 per cent in food consumption. This indicates that the borate was more detrimental than the iodide, the latter being more favorable to growth, under the otherwise unfavorable circumstances of reduced food consumption by the same group of rats. The results with the borate confirm what is known from other sources about the detrimental effects on health from continued use of borated food.

Thallium—The most toxic of all the salts was thallium. All five rats died suddenly at the end of four months, and all had showed the typical depilatory action at the end of six weeks, after the beginning of the administration. When one considers the severe effects produced, the changes in body weight and food consumption appeared proportionately small, but there may have been greater effects on specific functions or organs. Body weight was decreased 13 per cent and food consumption 16 per cent. Here, again, the lowered food intake could explain the nearly corresponding decrease in body weight or deficient growth. The sudden fatal termination was rather striking. The general appearance of the rats just before death was good, but the morbidity may have been greater than could be judged from external appearances. The depilatory and general injurious actions claimed by Buschke and Peiser⁷ and others are fully confirmed. As a hair-remover, the drug should be used cautiously, if at all. The results obtained with thallium served the usefulness of still another control on

the iodide action, for the rats of the same litter treated with iodide showed an increase of 6 per cent in body weight

Bromide—Sodium bromide caused a loss of 11 per cent in body weight but only 22 per cent in food consumption, suggesting that the diminished food intake was not wholly responsible for the greater loss in body weight. This haloid acted as a control for the iodide from the chemical standpoint. Pharmacologically, it acts differently. Whether the small daily doses employed could saturate the brain sufficiently so as to give some degree of depression (hypnotic action) is not known. The experiment lasted seven months, a period which is certainly long enough for saturation. However, lethargy or narcosis in the animals was not observed at any time.

It may be concluded that the chemically or pharmacologically related ions, sulphocyanate and bromide, in small continued doses corresponding to those of iodide cause opposite effects from iodide on body weight and growth of healthy rats on a complete diet, namely, a depression, an effect also caused by small, continued doses of arsenic, borate and thallium, and also by manganese in rats on a deficient diet. Thus, the action of these salts is in strong contrast to that of the iodide.

COMMENT

The results that we obtained with small doses of iodide agree with the augmentor effects on growth and correlated functions of similar doses observed by others. Our results corroborate those of Mačela⁹ on rats. Mačela found that daily doses of 0.2 mg of sodium iodide added to food caused faster gains in body weight than among controls, the treated rats also showed a more rapid sexual development. The results agree with those of Evvard and Culbertson¹⁰ on pigs receiving food containing 0.01 per cent potassium iodide, the pigs receiving medicated food gained an average daily increase of 10 per cent in body weight, thus indicating the economic possibilities of iodide for feeding livestock. Increased growth of yeast treated with low concentrations of iodide (from 0.001 to 0.5 per cent) has been reported by Scharrer and Schwartz¹¹.

The results obtained correlate with the lasting depressant effects of small doses (from 0.5 to 10 mg) of iodide on the metabolism of rats observed by Hildebrandt,¹² large doses gave the opposite effect. Depressant effects of small doses of iodide on metabolism in man

9 Mačela *Čas lek Česk* **64** 1551, 1925

10 Evvard and Culbertson *Research Bulletin of Iowa Agricultural Experiment Station* **80** 183, 1925

11 Scharrer and Schwartz *Biochem Ztschr* **187** 159, 1927

12 Hildebrandt *Arch f exper Path u Pharmacol* **96** 292, 1923

have been reported by Loewy and Zondek¹³ and by Neisser¹⁴. Hence, it would appear that the increased body weight resulting from the administration of small doses of iodide was the result of a retarded or depressed metabolism. Since the consumption of food was identical in our rats receiving iodide and the control rats, the increase in body weight was not due to more eating or a better appetite but to a direct action of the iodide on the tissues. Januschke¹⁵ pointed to iodide as being both a sedative and a stimulant according to the dosage or concentration for different organisms or tissues, and asserted that small doses of iodide (0.5 Gm twice daily) increase the body weight while larger doses decrease it. That large doses increase metabolism and reduce body weight has been adequately demonstrated. Recently, Grabfield¹⁶ concluded from his extensive studies of iodide that the increased metabolism is mediated through the thyroid gland. There is no reason to invoke this mechanism for small doses of iodide in healthy subjects. Comparing bromide and chloride with iodide, all in large doses, Hesse¹⁷ demonstrated the greatest increase in the metabolic rate of cats, rabbits and dogs with iodide; sulphocyanate did not increase the metabolic rate. Differences between the bromide and sulphocyanate ions were demonstrated also in our work. A more extensive discussion of the opposite metabolic actions of small and large doses of iodide will be found in a recent review by Burgi¹⁸.

It is of interest to note that during the past three years a number of investigators¹⁹ have reported the beneficial effects of small doses of iodide on the production of milk in cattle, a matter of some importance in child welfare. Daily doses of from 1.53 to 3.82 mg in salt or feed given to cows or goats improved the quality and increased the quantity of milk; this milk increased the growth of young rats 20 per cent over the controls, although it was claimed to be practically free from the iodide ion, it was not harmful to infants. Likewise, pigs nursed by sows receiving iodized food attained a much greater body weight at the time of weaning than those of mothers which had not received medi-

13 Loewy and Zondek. *Deutsche med Wchnschr* **47** 349, 1921

14 Neisser. *Berl klin Wchnschr* **57** 461, 1920

15 Januschke. *Weim med Wchnschr* **76** 1498 1926

16 Grabfield. *Boston M & S J* **197** 1121, 1927

17 Hesse. *Arch f exper Path u Pharmacol* **102** 63, 1924

18 Burgi. *Heffter-Heubner Handbuch f exper Pharmacol* **3** 366, 1927

19 Stiner. *Schweiz med Wchnschr* **55** 670 1925, **57** 846, 1927. Strobel and Scharrer. *Biochem Ztschr*, **180** 300, 1927. Scharrer and Schwaibold. *Biochem Ztschr* **180** 307, 1927. Strobel, Scharrer and Schropp. *Biochem Ztschr* **180** 313, 1927. Schwaibold and Scharrer. *Biochem Ztschr*, **180** 334, 1927. Scharrer. *Ztschr f d ges exper Med* **56** 677, 1927. Kieferle Kettner, Zuler and Hanusch. *Milchwirt, Fortschr* **4** 1, 1927. Maurer and St. Diez. *Biochem Ztschr* **182** 291, 1927.

cation²⁰ The increase in production of milk would appear to be intimately associated with the conservation of general metabolic processes, but whatever the mechanism, the collective results cited indicate that continued small doses of iodide are beneficial to the organism, thus emphasizing also the biologic rôle of this ion

CONCLUSIONS

1 The continued administration of iodide in small daily doses in food over long periods (covering from about one seventh to seven twelfths of the span of life) to rats caused moderate though variable increases in weight and growth of the body in the majority of animals on complete dietary The same tendency was indicated in rats on a deficiency diet

2 The dosage of iodide employed corresponded to that which may be employed under clinical conditions, but was probably greater than that used as iodized table salt

3 In contrast to the results obtained with iodide were those with sulphocyanate, bromide, arsenic, thallium and manganese, as controls, under the same conditions, these salts reduced body weight and growth, and arsenic and thallium caused fatalities

4 The results obtained with the iodide corroborate and correlate with interesting and important results obtained with small doses of iodide reported in the literature of veterinary medicine

5 Hence, there is no reason to believe from these experiments that the prolonged use of iodide in small doses under ordinary conditions is detrimental On the contrary, the results along various lines indicate that it is beneficial This would not apply to the continued use of iodide in specific conditions of the thyroid, or to large doses of the drug

20 Weiser and Zatschek *Biochem Ztschr* **187** 377, 1927

THE INHERITANCE OF MIGRAINE*

WILLIAM ALLAN, M D

CHARLOTTE, N C

There are few maladies that cause in the aggregate as much suffering as migraine, and about which so little is known concerning either causes, mechanism, prevention or cure. By migraine I mean any headache beginning in early life, recurring regularly or irregularly over a long period of years, without a discoverable pathologic process and without materially affecting the general state of health, such headaches are predominantly frontal and unilateral and are accompanied by nausea and vomiting, soreness of the eyeballs and scalp and in the majority of persons at some time by flitting scotoma or other sensory symptoms. The hereditary nature of migraine, since it is the subject of this study, has been purposely left out of the definition just given, but any consideration of the subject will always show that, next to pain in the head during attacks, the history of similar attacks in parents and in other members of the family is its most constant feature.

Living¹ credited Tissot² with being the first to emphasize the hereditary factor in migraine, but, as Smith³ pointed out, its familial occurrence had been the subject of comment since the beginning of the eighteenth century. Smith reviewed the gradual rise in the figures of parental history of migraine from 1858, when Symonds⁴ reported that 44 per cent of migrainous persons gave a history of headache in one or both parents. During the next half century, Living, in 1873, reported 50 per cent, Henchen,⁵ in 1881, reported 64 per cent, Moebius,⁶ in 1894, reported 90 per cent and Auerbach,⁷ in 1912, reported almost 100 per cent. In his own investigations, Smith found that when he could personally interview the parents of his migrainous patients, he always found migraine in them.

* Read before the Joint Session of the Eugenics Research Association and the American Eugenics Society, New York, June 2, 1928.

1 Living, E. *Megrim, Sick Headache and Allied Disorders*, London, J & A Churchill, 1873.

2 Tissot. *Traite des Nerfs et de leur Maladies*, Boyle's ed, 1834, p 383.

3 Smith, Jens. *Om Migraeneus Arveligheds forhold*, Bibliot f Laeger, August, 1922, p 310.

4 Symonds. *Gulstonian Lectures*, M Times & Gaz 1858, p 498.

5 Henchen S E. *Studier oefver Hufondets Nevralgier*, Upsala, 1881.

6 Moebius. *Die Migraine*, Vienna, 1903.

7 Auerbach, S. *Headache* translated by E Plavfair, London, Oxford University Press, 1913, p 36.

Along with this clinical observation pointing toward the direct inheritance of migraine, a number of impressions that do not correspond at all with direct inheritance of any sort have become firmly fixed in the literature of migraine. The commonest of these discordant factors is the marked preponderance of women in the various series of case reports. However, a statistical study⁸ of the sex ratio in migraine shows that men and women are affected in equal numbers, making it unnecessary to predicate any form of sex linkage.

A second erroneous clinical impression, often repeated, is that brain workers are more subject to migraine than those who work with their hands. A statistical study⁹ of the occupations of 400 persons with migraine failed to show that occupation bore any relation to its incidence.

A third impression is that in passing from generation to generation, migraine may appear as, or come from, a number of other conditions, ranging all the way from cancer and diabetes through the psychoses to epilepsy. A statistical study¹⁰ of 400 migrainous persons showed that psychoses, psychoneuroses and epilepsy were not any more frequent among migrainous than among nonmigrainous persons.

Up to the present time, few attempts have been made to correlate the observations on the familial occurrence of migraine with the laws of heredity originally discovered by Mendel.

In 1920, Buchanan¹¹ concluded that migraine is hereditary in accordance with Mendel's laws but did not consider the question of its dominance or recessiveness. His evidence is as follows: (a) in 100 families in which one parent was migrainous and which contained 631 children, 143 (22.66 per cent) had migraine, (b) in 17 families in which neither parent was migrainous and which contained 115 children, 30 (26 per cent) had migraine, this situation can be explained only on the assumption that migraine is recessive, and that all the parents in this group were heterozygous for migraine, (c) in three families in which both parents were migrainous and which contained fifteen children, all (100 per cent) had migraine. This group might represent matings of either pure dominants or pure recessives and does not give any evidence on the question of dominance. Part of Buchanan's evidence points to migraine as a recessive trait, and part of his data does not give evidence either way.

⁸ Allan, W., to be published.

⁹ Allan, W. The Relation of Occupation to Migraine, *J Nerv & Ment Dis* **66** 131 (Aug.) 1927.

¹⁰ Allan, W. The Neuropathic Taint in Migraine, *Arch Neurol & Psychiat* **18** 587 (Oct.) 1927.

¹¹ Buchanan, J. A. The Mendelianism of Migraine, *M Rec* **98** 807 (Nov 13) 1920.

In 1922, Smith³ stated (a) that a hereditary trait should be more prevalent among siblings of the possessor of such a trait than in the general population. This would vary with the incidence of the trait in the general population. In the case of migraine, if one uses my figures of 60 per cent incidence, the trait should be found in 77.8 per cent of the siblings, if dominant, and in 78.7 per cent, if recessive. Thus it will be seen that the incidence of migraine in siblings in this study could be of value in showing the hereditary nature of the malady but not in differentiating between dominance and recessiveness. Smith found the incidence in 158 women to be 37, or 23.5 per cent, and the incidence among 133 siblings to be 61, or 45.8 per cent.

Smith further stated (b) that direct parental inheritance points toward a dominant trait, but this is doubtful evidence, as it will be seen from tables 1 and 2. There will be parental headache in 100 per cent of the instances if it is a dominant trait, or if headache is recessive, accepting the incidence as 60 per cent, there will still be parental head-

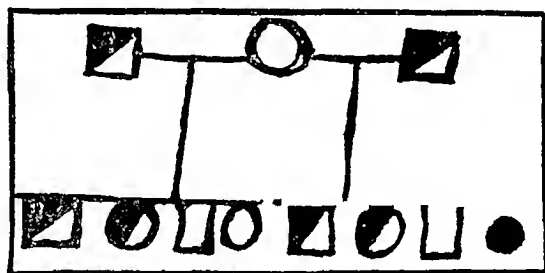


Fig 1—Inheritance of migraine. The white areas show migraine (recessive) and the black areas, normal (dominant).

ache in 95 per cent of the instances (in table 2), one fourth of matings 5, one half of 6, one half of 8, and 9 giving 60 per cent incidence, one fourth of 5 giving only 3, or 5 per cent, without parental headache.

Smith said (c) that the recurrence of headache in four or five successive generations points toward a dominant trait, but this is not always true, for with the incidence of migraine as high as it is, even though it were a recessive trait, 78 per cent of the matings among the general population would show migraine in both parents and children (table 2, matings 6, 8 and 9).

Smith said (d) that if a migrainous person marries twice, each mate being nonmigrainous yet both sets of children having migraine, this points toward a dominant trait. But if migraine is recessive and a migrainous person should marry two mates heterozygous for migraine, half of each set of children would have migraine. Under the known high incidence of migraine, this would be probable as well as possible.

Smith's evidence is largely for dominance though partly (b, c and d) inconclusive. He concluded that migraine is a dominant trait that in some way is sex determined.

The present conception of hereditary traits, based on the original laws of Mendel, is that such traits may be inherited as unit characters—the tallness of garden peas, for example, with its opposite shortness being the only possibility, as in complete dominance blending of such opposed traits does not occur. Since the work of Wilson,¹² Morgan¹³ and others, there has been a rational explanation of the physical basis of heredity in the packets of chromatin called genes which compose the chromosomes, one chromosome of each pair in any individual being derived from each parent. Thus if tall and short peas are crossed, their offspring will inherit tallness from one parent and shortness from the other, and as tallness is dominant in this cross all of this generation of hybrids will be tall. In the maturation of the germ cells in heterozygous individuals such traits segregate, half of the germ cells receiving

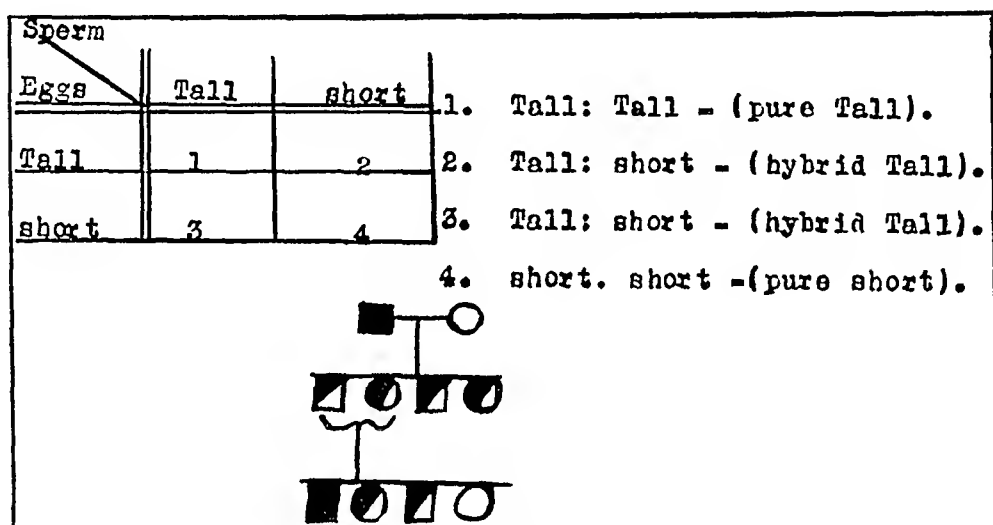


Fig 2—Crossing of hybrid peas, showing chance union of germ cells

one trait, the other half the opposite trait. Thus, the germ cells of the hybrid peas would contain genes for tallness or for shortness in about equal numbers. When such hybrids are crossed the chance union of the germ cells results, as illustrated in figure 2.

If migraine is hereditary, the question of dominance or recessiveness is the first to arise. This is attacked first on the general aspect of the data, and later on a statistical basis. From a general consideration of the families, the answer is not immediately forthcoming, due to several facts. First, migraine is a subjective phenomenon which cannot be mechanically measured. Second, its allelomorph is not a definite character but is simply the absence of headache. There are headaches of many

12 Wilson, E. B. *The Cell In Development and Heredity*, ed 3, New York, The Macmillan Company, 1925.

13 Morgan, T. H. *The Theory of the Gene*, New Haven, Yale University Press, 1926.

sorts, and in any series of headaches thought to be hereditary there will be some error in diagnosis. Thus the usual criteria of dominance and recessiveness—purity of the germ cells of the recessive type, absence of recessive offspring when one parent is homozygous dominant, etc.—are not practicable in this case. It is necessary to treat the data statistically, comparing the observed figures with the expected results and considering the character first as a dominant, then as a recessive.

To determine the incidence of migraine in the general adult population, 282 men taken consecutively were asked about headache and a positive history of migraine obtained in 57.4 per cent. In the same way, 62.6 per cent of 348 women gave a positive history of migraine. In view of the mild character and infrequency of attacks of migraine in some persons, this average incidence of 60 per cent will be somewhat below the real incidence.

It is evident that in dealing with a hereditary trait it is necessary to know the relative frequencies of the factors concerned and from these to calculate the relative occurrence of homozygous dominants, heterozygous dominants and recessives. Then, and only then may tables be constructed showing the statistical results to be expected in mass matings of various types. The frequencies of the factors concerned, if migraine is first considered as a dominant and then as a recessive and my figures of 60 per cent occurrence of migraine in the general population being used, are as follows:

If migraine is dominant

Let M = gene for migraine
then m = gene for normal condition

And let p = frequency of M
and q = frequency of m

Then $p + q = 1$

The possible combinations of these factors are expressed by the equation $(p+q)^2=1$. From this, the following combinations are formed:

	M	m
	p	q
M	MM	Mm
p	p^2	pq
m	Mm	mm
q	pq	q^2

$p^2 + 2pq = \text{migrainous persons}$
 $q^2 = \text{nonmigrainous persons}$
 $q = \sqrt{\text{nonmigrainous persons}}$

Substituting the figures that I have found for nonmigrainous persons, one has

$$q = \sqrt{40} = 0.632$$

$$p = 1 - q = 0.368$$

Substituting values of p and q in the foregoing equations, one has

p^2 = Homozygous migrainous persons	13.5 per cent (MM)
$2pq$ = Heterozygous migrainous persons	46.5 per cent (Mm)
q^2 = Nonmigrainous persons	40.0 per cent (mm)

Within the migrainous persons, there are the following relations

Homozygous migrainous	22.5 per cent (MM)
Heterozygous migrainous	77.5 per cent (Mm)

If migraine is recessive,

Let M = gene for normal condition
then m = gene for migraine

And let p = frequency of M

and q = frequency for m

Then $p + q = 1$

The possible combinations of these factors are expressed by the equation $(p+q)^2=1$. From this, the following combinations are formed

	M	m
M	p	q
p	MM	Mm
m	p^2	pq
q	Mm	mm
	pq	q^2

$p^2 + 2pq$ = nonmigrainous persons

q^2 = migrainous persons

$q = \sqrt{\text{migrainous persons}}$

Substituting the figures that I have found for migrainous persons, one has

$$q = \sqrt{60} = 0.774$$

$$p = 1 - q = 0.226$$

Substituting values of p and q in the foregoing equations, one has

p^2 = Homozygous nonmigrainous persons	5.0 per cent (MM)
$2pq$ = Heterozygous nonmigrainous persons	35.0 per cent (Mm)
q^2 = Migrainous persons	60.0 per cent (mm)

Within the nonmigrainous persons are the following relations

Homozygous nonmigrainous,	12.5 per cent
Heterozygous nonmigrainous,	87.5 per cent

Migraine in the general population is represented in tables 1 and 2

STATISTICAL REQUIREMENTS

If migraine is a true mendelian unit character, it will fulfill certain statistical requirements relative to its occurrence in parents, children and siblings. These requirements have been calculated on the basis of migraine as both a dominant and as a recessive the frequencies derived in the foregoing tables being used. My figures are compared with the statistical requirements in each case.

1 When both parents have migraine, the percentage of migraine in the children should be, if dominant, 84.9 and if recessive, 100 (table 3) My figures are 83.3 per cent

TABLE 1—Incidence in General Population If Migraine Is Dominant

	MM 135	Mm 465	mm 400
MM	1	2	3
135	018	063	054
Mm	4	5	6
465	063	216	186
mm	7	8	9
400	054	186	100
1 MM × MM	—	MM MM MM MM	1.8%
2 MM × Mm	—	MM MM Mm Mm	6.3
3 MM × mm	—	Mm Mm Mm Mm	5.4
4 Mm × MM	—	MM MM Mm Mm	6.3
5 Mm × Mm	—	MM Mm Mm mm	21.6
6 Mm × mm	—	Mm Mm mm mm	18.6
7 mm × MM	—	Mm Mm Mm Mm	5.4
8 mm × Mm	—	Mm Mm mm mm	18.6
9 mm × mm	—	mm mm mm mm	16.0
			100.0

TABLE 2—Incidence in General Population If Migraine Is Recessive

	MM 05	Mm 35	mm 60
MM	1	2	3
05	0025	0175	0300
Mm	4	5	6
35	0175	1225	2100
mm	7	8	9
60	0300	2100	3900
1 MM × MM	—	MM MM MM MM	0.25%
2 MM × Mm	—	MM MM Mm Mm	1.75
3 MM × mm	—	Mm Mm Mm Mm	3.00
4 Mm × MM	—	MM MM Mm Mm	1.75
5 Mm × Mm	—	MM Mm Mm mm	12.25
6 Mm × mm	—	Mm Mm mm mm	21.00
7 mm × MM	—	Mm Mm Mm Mm	3.00
8 mm × Mm	—	Mm Mm mm mm	21.00
9 mm × mm	—	mm mm mm mm	36.00
			100.00

TABLE 3—Incidence of Migraine When Both Parents Have It (Migraine Dominant)

	MM 0.225	Mm 0.775		1 MM MM MM MM	5.1%	% MM	% Mm	% mm
MM	1	2	2 MM MM Mm Mm	17.4	5.1			
0.225	0.651	0.174	3 MM MM Mm Mm	17.4	8.7	8.7		
Mm	3	2	4 MM Mm Mm mm	60.1	8.7	8.7		
0.775	0.174	0.601			15.0	30.0	15.0	
					37.5	47.4	15.0	
						84.9		

TABLE 4—Incidence of Migraine When One Parent Has It (Migraine Dominant)

	MM 0.225	Mm 0.775		1 Mm Mm	22.5%	% Mm	% mm
mm	1	2	2 Mm mm	77.5	22.5	38.75	38.75
1.00	0.225	0.775			38.75	61.25	38.75

TABLE 5—Incidence of Migraine When One Parent Has It (Migraine Recessive)

	MM 0.125	Mm 0.875		1 Mm Mm	12.5%	% Mm	% mm
mm	1	2	2 Mm mm	87.5	12.5	43.7	43.7
1.00	0.125	0.875			43.7	56.2	43.7

2 When only one parent has migraine the percentage of migraine in the children should be if dominant, 61.2 and if recessive 43.7 (tables 4 and 5) My figures are 61

3 When neither parent has migraine, the percentage of migraine in the children should be, if dominant, 0 and if recessive, 19.1 (table 6). My figures are 3.7 per cent

4 There should be a history of migraine in one or both parents of migrainous children if dominant, in 100 per cent (table 1), matings (1 to 8) and if recessive, in 95 per cent (table 7). My figures are 91.4 per cent

TABLE 6—Incidence of Migraine When Neither Parent Has It (Migraine Recessive)

	MM 0.125	Mm 0.875				% MM	% Mm	% mm
MM	1	2	1	MM MM MM MM	1.6%	10.9	10.9	
0.125	0.016	0.109	2	MM MM Mm Mm	10.9	19.1	38.3	19.1
			3	MM MM Mm Mm	10.9			
Mm	3	4	4	MM Mm Mm mm	76.6	31.6	49.2	19.1
0.875	0.109	0.766						

TABLE 7—Incidence of Migraine When One or Both Parents Have It (Recessive)

Table 2, One half of matings 6 = 10.50
One half of matings 8 = 10.50
Matings 9 = 36.00
Total incidence 60] 57.00 { 0.95

TABLE 8—Incidence of Migraine When Both Parents Have It (Dominant)

Table 1, mating 1 = 1.8
Mating 2 = 6.3
Mating 4 = 6.3
Three fourths mating 5 = 16.2
Total incidence 60] 30.6 { 0.51

TABLE 9—Incidence of Migraine When One Parent Has It (Dominant)

Table 1, mating 3 = 5.4
One half of mating 6 = 9.3
Mating 7 = 5.4
One half of mating 8 = 9.3
Total incidence 60] 29.4 { 0.49

TABLE 10—Incidence of Migraine When One Parent Has It (Recessive)

Table 2, one half mating 6 = 10.50
One half mating 8 = 10.50
Total incidence 60] 21.00 { 0.35

5 Both parents of migrainous children should have migraine if dominant, in 51 per cent (table 8) and if recessive, in 60 per cent (in table 2), only in mating 9 are both parents migrainous=36 per cent of 60=60 per cent. My figures are 26 per cent

6 Only one parent of the migrainous should have migraine if dominant, in 49 per cent (table 9) and if recessive, in 35 per cent (table 10). My figures are 60 per cent

7 Neither parent of migrainous children should have migraine if dominant, in 0 per cent (table 1) and if recessive, in 5 per cent (table 2) one fourth of mating 5, 3 in 60=5 per cent My figures are 86 per cent

8 Siblings of migrainous persons should have migraine if dominant, in 77.8 per cent (table 11) and if recessive, in 78.7 per cent (table 12) My figures are 67.2 per cent

TABLE 11—*Incidence in Siblings of Migrainous (Dominant)*

Table 1, mating 1 = 1.8 migrainous siblings	100% = 1.8
Mating 2 = 6.3 migrainous siblings	100% = 6.3
Mating 3 = 5.4 migrainous siblings	100% = 5.4
Mating 4 = 6.3 migrainous siblings	100% = 6.3
Three fourths of mating 5 = 16.2 migrainous siblings	75% = 12.2
One half of mating 6 = 9.3 migrainous siblings	50% = 4.65
Mating 7 = 5.4 migrainous siblings	100% = 5.4
One half of mating 8 = 9.3 migrainous siblings	50% = 4.65
Total incidence 60] 46.70 [77.8	

TABLE 12—*Incidence in Siblings of Migrainous (Recessive)*

Table 2, One fourth of mating 5 = 3.08 migrainous siblings	25% = 0.77
One half of mating 6 = 10.50 migrainous siblings	50% = 5.25
One half of mating 8 = 10.50 migrainous siblings	50% = 5.25
Mating 9 = 36.00 migrainous siblings	100% = 36.00
Total incidence 60] 47.27 [78.8	

TABLE 13—*Incidence in Siblings of Nonmigrainous (Dominant)*

Table 1, One fourth of mating 5 = 5.4, with 75% migrainous	= 4.05
One half of mating 6 = 9.3, with 50% migrainous	= 4.65
One half of mating 8 = 9.3, with 50% migrainous	= 4.65
Total incidence 40] 13.35 [33.4	

TABLE 14—*Incidence in Siblings of Nonmigrainous (Recessive)*

Table 2, Three fourths of mating 5 = 9.18, with migrainous siblings	25% = 2.3
One half of mating 6 = 10.50, with migrainous siblings	50% = 5.25
Mating 8 = 10.50, with migrainous siblings	50% = 5.25
Total incidence 40] 12.80 [32	

9 Siblings of the nonmigrainous should have migraine if dominant, in 33.4 per cent (table 13) and if recessive, in 32 per cent (table 14) My figures are 11.5 per cent

CLINICAL DATA

The statistics used here except items 3 and 9, were taken from a review of 500 of my cases of migraine. The actual clinical data are as follows

1 In 56 families in which both parents were migrainous and which contained 318 children, 240 had migraine, 48 did not and in 30 the history was not known or the children were too young, giving a positive figure of 83.3 per cent

2 In 141 families in which one parent was migrainous and one not and which contained 750 children, 342 had migraine and 217 did not, in 191, the history was not known or the children were too young. This gives a positive figure of 61 per cent. In 99 families in which one parent was migrainous and the history of one unknown and which contained 517 children, 266 were migrainous, 153 were not and in 152 the history was not known. This gives a positive figure of 63.4 per cent. If one combines these two groups one has 240 families in which it was known that one parent had migraine. Of the 978 children about whom data were available, 62 per cent had migraine.

3 In 98 families in which neither one of the parents had migraine, containing 485 children, 18, or 3.7 per cent, had migraine.

4 A history of migraine in one or both parents was given in 349 (91.4 per cent) of 382 migrainous patients.

5 Data on both parents were obtained from 243 patients, and in 63 instances (26 per cent) both parents were said to have migraine.

6 A history of migraine in one parent but not in the other was given in 147 (60 per cent) of 243 migrainous patients.

7 A history of migraine in neither parent was given in 33 (8.6 per cent) of 382 migrainous patients.

8 In the families of 376 migrainous patients containing 2,105 children, 658 siblings had migraine, 504 did not have it, and in 567 the history was not known or the children were too young. This gives an incidence of 67.2 per cent of the 1,538 children about whom data were available.

9 In 163 family histories given by children who did not have headache themselves, 90, or 11.8 per cent, of a total of 911 children are said to have migraine, 722 to be without migraine, and in 99 the history was not known.

The information about headache in parents and siblings secured from persons who did not themselves have headache, as in items 3 and 9 is probably not reliable. The figure in item 7 represents the same supposed error as recorded in item 4. The figures in items 5 and 6 might be changed on more accurate information about both parents.

The genetic and statistical evidence presented in this paper indicates that migraine is inherited as a dominant unit mendelian character.

EFFECT OF ADMINISTRATION OF MEDICINAL IRON ON THE IRON RESERVE

AN EXPERIMENTAL STUDY ^k

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AND

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CHICAGO

In a previous publication ¹ we gave the results of some experiments on the iron reserve in animals, first as affected by the standard casein diet, and second as affected by the feeding of food known to be rich in available iron. While it is commonly stated that the body does not have any reserve of iron in the same sense that it has reserves of calcium and phosphorus, there are many clinical facts which make it seem likely that there must be at least enough iron in reserve to take care of the ordinary contingencies of everyday life. Relatively prompt recovery of animals and human beings after bleeding, even when the iron in the diet is not especially abundant, would seem to make this point apparent. The experiments referred to were undertaken with the idea of determining in a positive manner whether this surmise is correct, and whether an iron reserve really does exist, and if so to obtain at least an approximate idea of the amount of such a reserve, and of the readiness with which it may be drawn on for the repair of losses of iron such as occur in hemorrhages. Since the present work is a direct extension of our previous experiments, a brief synopsis of the results of these will be here given.

Our plan of procedure was as follows. A large number of white rats was obtained and divided into two groups in such a way that the litters were divided, half of the young being in one group, and the other half being used as controls. One group was kept on the standard casein diet, the other group on the same diet, which was modified, in that a portion of the protein was obtained from dried beef liver instead of casein, the caloric and protein content of the whole remaining the same. Both of these diets were adequate in all respects. We have numerous charts which show that the growth curve was entirely normal. The young were reared successfully, the litters were full sized and the young in their turn grew normally, bred at the usual time and in their turn reared full sized litters of normal young. The hemoglobin content was

^k From the Department of Medicine, University of Illinois College of Medicine.

¹ Williamson, C. S. and Ets, H. N. The Problem of the Iron Reserve. Arch Int Med 40 668 (Nov.) 1927.

determined immediately before the rats were placed on the diets, and then at intermediate times, after they had been on the diets up to four months

Before the experiments were begun, the two groups showed practically identical concentrations of hemoglobin, namely 0.77 for the group to be placed on liver diet and 0.766 for the control group. After the animals had been on their respective diets for a little more than three months, the percentage of hemoglobin had increased materially in both groups, as is normally the case with young animals. The figures were 1.11 and 1.091. It is clear, then, both from these figures and from our previous work that the feeding of normal young rats with a diet which contains available iron in amounts far above their metabolic needs does not increase the amount of hemoglobin in the blood. This, in view of what is known of the constitution of the blood, was to be expected. Our train of thought was as follows. If the body is capable of storing up iron outside of the circulation, in a form available for use when there is a drain on the circulating iron, for instance, after hemorrhage, it would follow that if these two groups of animals were each bled identical amounts, the animals which had been fed on food rich in iron might recover from the effects of these hemorrhages more quickly than the animals on ordinary diets. Conversely, if, after the two groups had been bled to the same extent, one group should recover more quickly or to a greater extent than the control group, this fact would constitute the best possible proof that an iron reserve had been stored up and was capable of being used in the replacement of the lost blood. Our results in these experiments were striking and decisive. We began, as already stated, with identical concentrations of hemoglobin in both groups, six days after bleeding, we found that the group on the liver diet showed a concentration of 0.927, whereas the control group, on the casein diet, showed a concentration of only 0.745. At the end of twenty-eight days after bleeding, the group on the liver diet showed a concentration of 1.033, whereas the group on the casein diet showed only 0.735. These results were so striking as to admit of only one interpretation, namely that there is a definite storage of iron in a readily available form amounting, under our conditions of experiment, to about 30 per cent. These results were further checked by determinations of iron in the liver and spleen in groups of twenty animals on each diet before bleeding and after bleeding. Before bleeding the rats on the liver diet showed 22.2 mg.² of iron in their livers, and 51.2 mg. of iron in the spleen as compared with 14.2 and 21.3 mg. in the animals fed on casein. Determinations of iron in the liver and spleen were also

2 All values of iron are expressed in milligrams of iron per hundred grams of tissue

made twenty-eight days after bleeding with the following results liver, 13.3 mg, spleen, 29.5 mg in the animals fed with liver, as compared with 9.9 and 14.1 mg, respectively, in the group fed with casein. By subtracting the figures after bleeding from those obtained before bleeding, it is plain that the animals on the liver diet lost 8.9 mg from their livers and 21.7 mg from their spleens, as compared with 4.3 and 7.2 mg, respectively, in the animals on the casein diet. These figures demonstrate conclusively, we think, not only that the storage is largely in the liver and spleen, but that these organs store the iron in a readily available form. Of course, it is possible, indeed probable, that much of the iron in these two organs is present in a form not available for conversion into hemoglobin. Our ¹ previous experiments seem to show this clearly.

If it is accepted, then, as a demonstrated fact, that there is a substantial reserve of available iron in the organism which may amount, under conditions of experiment similar to ours, to as much as 30 per cent, then the further question naturally suggests itself, Is it possible to produce a reserve supply of available iron by the systematic feeding of ordinary medicinal iron in the place of the iron in the food?

It need hardly be pointed out that the matter is one of considerable practical, as well as theoretical, importance. In view of the admitted difficulties in the way of arranging a diet either for children or for adults, which contains a sufficiency of available food iron, it would be a tremendous help if the ordinary forms of medicinal iron could take the place of this food iron in building up a reserve. If it should prove that medicinal iron were even measurably efficient in storing up a reserve of available iron we could, perhaps, afford to give less thought to the diet, at least so far as its containing a sufficient amount of food iron is concerned.

METHODS

Our experiments were conducted along the same lines as those followed in the work already mentioned. A large number of young, white rats was obtained in litters of from six to ten. The litters were so divided that half of the animals in each litter were used for the iron feeding experiments while the other half were used as controls. We feel that it is most important to use a large number of animals, and to use as many controls as there are animals to experiment with. This is a point that is too often overlooked in such work. Our plan of procedure was as follows. The concentration of hemoglobin of the blood was taken before the rats were placed on the diet, which was identical in the two groups, except that in one, which we called the "iron diet group" we added ferric citrate. After the animals had been on their respective diets for ninety days, the concentration of hemoglobin was again taken. Immediately after the second determination, each animal was bled 25 per cent of the calculated volume of blood directly from the heart. The concentration of hemoglobin was then again taken on each animal on the sixth and twenty-eighth day after it had been bled. It is not necessary to refer in detail to the methods employed, since they have been described at length

TABLE 1—Results of Experiments on White Rats

Rats on Iron Free Diet					Rats on Iron Diet				
Rat Num- ber	Before Bleeding		After Bleeding		Rat Num- ber	Before Bleeding		After Bleeding	
	June 27	Sept 27	6 Days	27 Days		June 27	Sept 27	6 Days	27 Days
3	0.921	1.236	0.999	1.185	1	0.915	1.149	1.068	1.049
7	0.946	0.968	0.895	0.934	2	0.842	0.891	0.992	1.004
8	0.938	1.078	1.032	1.239	3	0.955	0.907	0.838	
9	0.834	0.911	0.652	0.983	6	1.004	1.180	0.632	1.049
10	0.858	1.093	0.957	1.191	11	0.790	1.104	1.032	1.029
15	0.662	0.942	1.032	1.053	12	0.999	1.066	1.039	0.958
18	0.839	1.051	0.756	1.052	13	0.906	1.039	0.968	1.013
22	0.838	1.004	0.768	1.008	14	0.929	0.934	1.034	0.962
26	0.936	1.051	0.903	1.056	16	0.951	0.992	0.701	0.939
31	0.847	1.058	0.645	1.039	17	1.006	0.878	0.897	1.160
33	0.999	1.076	0.870	1.168	19	0.923	1.215	1.073	1.025
34	0.942	1.066	0.864	1.218	20	1.036	1.004	0.689	0.958
35	0.951	1.025	0.862	0.990	21	0.907	1.135	0.946	1.051
36	1.044	0.936	0.921	1.018	23	0.955	1.056	0.642	1.103
38	1.109	0.938	0.741	1.071	24	1.015	1.149	0.946	1.032
40	1.039	0.891	0.768	0.953	27	0.997	1.013	0.970	0.964
43	0.955	1.163	0.756	1.083	28	0.921	1.124	1.022	1.135
44	0.921	1.086	0.995	1.206	32	0.600	0.940	0.946	0.891
46	0.917	1.044	0.834	1.063	37	0.927	1.066	0.822	1.025
49	0.905	1.110	0.944	1.242	39	0.807	1.027	0.932	1.010
52	0.780	1.036	0.751	1.053	41	0.923	1.223	1.001	1.020
55	0.966	1.109	0.913	1.135	42	1.010	0.981	0.809	1.078
57	0.923	1.093	0.847	1.046	45	0.934	1.078	0.842	0.862
58	0.921	1.098	0.923	1.141	47	0.813	0.938	0.911	0.881
60	0.938	1.053	0.979	1.182	53	0.885	1.041	0.683	1.006
61	1.051	0.958	0.793	1.239	54	0.883	0.961	0.966	1.127
62	1.006	0.713	0.849	1.043	56	0.988	1.063	0.921	1.141
64	1.081	1.041	0.915	1.160	63	1.081	0.847	1.049	1.223
65	0.944	1.068	0.891	1.143	66	0.901	1.073	0.990	1.146
68	1.046	1.053	0.957	1.185	67	0.966	1.093	0.678	1.034
70	0.968	1.135	0.925	1.125	69	0.940	1.114	0.988	0.992
72	0.907	1.122	0.990	1.165	71	0.955	1.088	1.053	1.091
73	0.938	0.860	0.895	1.149	77	0.956	1.076	0.921	1.032
74	0.983	1.061	0.713	1.010	78	0.949	0.936	0.940	1.041
75	0.936	1.270	1.010	1.071	79	0.909	1.008	1.049	1.119
76	0.927	1.053	1.027	1.111	81	1.111	1.078	0.946	
80	1.011	0.813	0.857		84	0.979	1.011	0.887	0.955
83	0.944	1.103	1.001	1.068	86	1.044	1.114	0.864	0.968
87	0.990	0.907	1.055	1.122	88	1.053	0.859	0.997	0.988
91	0.955	1.163	1.027	1.177	89	1.029	0.909	0.932	1.061
92	0.796	1.039	1.018	1.182	90	0.938	1.073	0.938	0.993
93	0.957	0.933	0.716	1.220	96	0.938	1.093	0.944	0.992
94	0.885	1.038	0.955	1.141	97	1.032	1.045	0.662	0.878
100	0.953	1.165	0.853	1.071	98	0.936	1.138	0.936	1.098
101	0.903	1.130	0.889	1.036	99	0.953	1.191	0.911	0.999
103	0.964	1.100	0.719	1.081	102	0.905	1.103	0.656	1.086
107	0.862	1.146	0.961	1.101	104	0.921	1.036	0.953	1.053
108	0.915	1.148	0.962	0.942	105	0.979	1.046	0.856	0.889
109	0.937	1.083	0.961	1.006	112	0.866	1.034	0.905	0.903
111	0.813	1.034	0.756	0.949	114	0.903	1.049	0.934	1.024
115	1.138	1.117	0.774	0.919	116	0.936	1.015	0.929	1.029
118	1.004	1.093	0.939	1.233	117	0.860	1.057	0.834	1.138
123	0.936	1.068	0.821	1.027	119	0.851	1.133	0.891	1.163
132	0.936	1.163	1.029	1.101	121	0.944	1.117	0.992	1.106
135	0.868	0.899	0.877	0.860	122	0.923	1.041	0.923	1.044
143	1.001	0.887	0.730	1.174	125	0.944	1.039	0.748	1.018
144	0.975	0.990	0.864	1.109	128	0.830	1.063	0.925	1.036
150	0.959	1.029	0.891	1.044	130	1.018	1.051	0.905	0.955
153	0.849	1.029	0.855	1.168	131	0.921	0.997	0.944	1.049
154	0.887	1.141	0.842	1.053	133	0.940	1.106	0.809	
156	0.940	0.956	0.879	0.855	134	0.889	0.940	0.816	0.874
159	0.853	1.039	0.872	1.138	136	0.942	1.093	0.979	1.013
161	0.955	1.116	0.805	1.106	138	1.081	1.041	0.769	0.899
162	0.874	1.101	0.778	1.041	141	0.997	1.053	0.949	1.038
164	1.024	1.093	0.951	1.119	145	0.949	1.083	0.797	0.997
165	0.907	1.029	0.882	1.094	146	0.990	1.044	0.953	1.088
166	0.883	1.135	0.816	1.041	151	0.990	0.919	0.895	0.829
169	0.919	1.098	0.889	1.071	155	0.863	0.983	0.698	0.795
171	0.903	1.146	0.889	1.071	157	0.975	0.935	0.738	0.864
175	0.981	0.932	0.711	1.088	158	0.961	0.938	0.665	0.879
177	0.864	1.098	0.911	0.990	160	1.039	1.013	0.944	1.105
179	0.975	1.114	0.919	1.114	163	1.063	0.917	0.708	0.883
180	0.931	1.114	0.953	1.101	172	0.957	1.024	0.891	1.034
181	0.979	1.020	0.847	0.997	173	0.856	1.044	0.903	0.917
183	0.911	0.946	0.725	0.849	174	0.919	1.071	0.842	1.063
184	0.949	1.124	0.866	1.066	176	1.046	1.076	0.903	1.001
186	0.923	0.934	0.602	0.979	178	0.849	1.032	0.842	0.942
187	1.015	1.073	0.955	1.182	182	0.928	1.044	0.741	0.929
192	0.878	1.168	0.876	1.051	185	0.972	0.823	0.681	0.600
					188	0.983	1.044	0.905	1.013
					190	0.975	1.049	0.876	1.049
					191	0.999	0.999	0.864	0.934
Average	0.934	1.051	0.874	1.084	Average	0.945	1.035	0.885	1.005

in a previous communication³ We adopted in this work, as before, the accurate spectrophotometric method, since it requires a minimal amount of blood, does not have any color standards to fade, and, if one has the proper command of the technic and a suitable apparatus, admits of an exceedingly accurate and fairly rapid determination of hemoglobin

RESULTS

Our results can be stated in a few words The average concentration of hemoglobin of the rats before being placed on the diet was 0.934 for the controls and 0.945 for the group to be placed on an iron diet After the rats had been on the diets for ninety days, the concentration of hemoglobin was 1.051 and 1.035 for the controls and for the rats fed on iron, respectively Such variations as these, amounting to 1 or 2 per cent, occur in any series of animals, even when on identical diets We have then again abundant confirmation of our previous results, namely, that it is not possible to increase the amount of hemoglobin in the blood in normal, young rats by feeding them ferric citrate in addition to their standard diet

On the sixth day after bleeding, we found that the concentration of hemoglobin was 0.874 and 0.885 for the controls and the groups fed on iron, respectively In other words, the two groups were substantially identical To make sure that there might not be a belated improvement, we again took the concentration of hemoglobin on the twenty-eighth day after bleeding, and found the concentrations to be 1.084 for the controls and 1.005 for the group fed on iron The question may arise as to whether a difference of approximately 8 per cent is within the probable limit of error, but in any event it is to the disadvantage of the group fed on iron From these figures, then, it will seem perfectly obvious that it is not possible by the administration of ferric citrate over a relatively long period of time to build up reserve of available iron, that is of iron capable of being converted into hemoglobin We did not make analyses of either the entire bodies of the rats or the livers or spleens, since we had done this and had published the results in detail in a previous communication,³ and had shown conclusively that there is a storing up of iron in the liver, spleen and bone marrow, but that, under our conditions of experiment, this iron was not capable of being converted into hemoglobin The fault lies not with the absorption of iron, as was supposed by Bunge and his followers, but with its ability to be converted into hemoglobin

The results obtained in the experiments just quoted stand in the most striking contrast to the results obtained under identical conditions in the group of animals which had been fed on food iron in quantities above their metabolic needs As already stated, there was, in this group,

³ Williamson, C. S., and Ets, H. N. Value of Iron in Anemia, *Arch. Int. Med.* **36**: 333 (Sept.) 1925

a storage of available iron to the extent of about 30 per cent. For the sake of clearness and easy comparison, the results are shown side by side in table 2.

An inspection of table 2 shows that whereas in the rats fed on food iron and on ferric citrate the concentration of hemoglobin was substantially identical in both the experimental and the control groups before they had been bled, on the sixth day after bleeding the ratio of the concentration in the group fed on ferric citrate was $\frac{0.885}{0.874}$, i.e., substantially identical, whereas in the animals fed on food iron, the ratio was $\frac{0.927}{0.732}$, a difference of more than 20 per cent. On the twenty-eighth day after bleeding, in the animals fed on ferric citrate, the ratio was $\frac{1.005}{1.084}$, an actual diminution, whereas in the rats fed on food iron, the ratio was $\frac{1.033}{0.785}$, a striking increase in favor of the animals fed on food iron.

TABLE 2—Comparison of Results with Food Iron and Ferric Citrate

	Results with Ferric Citrate			
	Before Being Placed on Diet	After Twenty Days on Diet	Bled 25 Per Cent of the Volume of Blood	Twenty Light Days After Bleeding
Iron group	0.945	1.035		1.005
Control group	0.934	1.051		1.084
	Results with Food Iron (Liver) in Livers			
Liver group	0.770	1.104		1.033
Control group	0.766	1.096		0.785

We may say, then, that it is readily possible for the organism to store a satisfactory reserve of iron, if there has been an excess of available food iron in the diet for a sufficient time. These results cannot be obtained by the simple addition of ferric citrate, however desirable this might be.

It cannot be definitely concluded that if the addition of ferric citrate cannot build up a reserve of available iron in a normal animal, it will not build up the concentration of hemoglobin in an animal which has a pathologically low concentration of hemoglobin. It is, however, most suggestive, and taken in combination with our previous work, we are inclined to see a confirmation of that work.

SUMMARY

1 Rats fed on the standard diet plus ferric citrate do not show an increase in the concentration of hemoglobin over rats on the same diet minus ferric citrate.

2 After 25 per cent of the volume of blood has been bled rats which have been fed ferric citrate in addition to the standard diet for a long

time before bleeding do not recover any more quickly than the control group which has not been given ferric citrate. Expressed in other words, the addition of ferric citrate to the diet of rats cannot build up a reserve of available iron, that is, of iron capable of being converted into hemoglobin.

3 This last result is in striking contrast to the results of our previous work, wherein it was shown that the feeding of food iron under the same conditions resulted in the storing up of approximately 30 per cent of reserve iron, which was immediately utilizable after a strain on the body, as, for example, after hemorrhage.

Book Reviews

TRATADO DE LA DIABETES By PEDRO ESCUDERO Pp 700 Buenos Aires
Libreria "El Alteneo," 1927

This book of about 700 pages covers the extent of the modern knowledge of diabetes. It is arranged in an orderly manner and treats thoroughly involved features of the chemistry of sugar metabolism. The presentation is clear and simple. It is not only a textbook for the student, but a handy reference book, the technic of all the necessary tests and chemical reactions being described throughout.

The material for this treatise comes from the large clinic of Escudero, who is professor of medicine in the University of Buenos Aires, and the result of much practical experience can be found in these pages.

The work is divided into four sections. The first section contains an elaborate discussion of sugar metabolism and its chemical features in both the normal and the diabetic person. Under this heading is included the relation of sugar metabolism to other foodstuffs, and the importance of the broader aspects of alimentation in diabetes is emphasized.

Section two covers the pathologic, physiologic and clinical aspects of glycosuria. In this section the portions dealing with the use of insulin are especially valuable.

The third section takes up the complications of diabetes and their management. Especially noteworthy here is the original work of Escudero on latent diabetes. He has shown that a number of diseases of the skin, the eyes and the nervous system are due to lack of power of oxidation of carbohydrates, which has not yet reached the stage of glycosuria. By careful studies of the metabolism of a number of such conditions and antidiabetic management he has brought about striking clinical cures.

The fourth section should really be published as a separate pamphlet. It is a "Guide for the Diabetic," and begins with a short description in simple terminology, that is comprehensive to the laity, it continues with the usual instructions for the patient as to his mode of life and dietary lists. This section is not of much value to the American public as so many of their foods are strange to us.

THE SIMPLE GOITER By ROBERT MCCARRISON Price \$4.00 New York
William Wood & Company

The contents of this book formed the subject matter of a report to the International Conference on Goiter held at Berne in August, 1927.

In the introduction, he discusses the normal physiology of the thyroid and its response to heat, cold, altitude, puberty and other factors, and emphasizes here as throughout the book that too much stress has been laid on deficiency of iodine as the dominant factor in enlargement of the thyroid of the adenomatous type. The two types of simple goiter—adenoma parenchymatous and diffuse colloid—he believes differ in their epidemiology and etiology. Deficiency of iodine may play an important rôle in colloid goiter. His studies, made in India, were almost entirely on the adenoma parenchymatous type. He believes deficiency of iodine is not the important etiologic factor. His experimental work on both animal and man, all of which has been previously published, suggests the presence of some toxic substance, probably bacterial. His clinical observation and experimental work were apparently carefully controlled and while his views have not been widely accepted, they are nevertheless convincing, and cannot be lightly discarded.

The last half of the book is given over to illustrations. There are charts showing the incidence of goiter before and after purifying the water supply, photographs of people with goiter and creatins, photographs before and after production of experimental goiter in man, another series showing the result of

treatment with intestinal antiseptic or protein shock therapy, and finally a series of photomicrographs of the thyroid in man and experimental animals. This volume, which contains the collected observations of a lifetime, is a valuable contribution concerning one man's experience with goiter.

HORMONE UND INNERE SEKRETION By DR FRITZ LAQUER, Privatdozent an der Universität Frankfurt A M. Price, 8 30 marks, paper, 10 marks, bound Pp 136, with index. Dresden and Leipzig: Theodor Steinkopff, 1928.

In the plethora of monographs on the endocrine glands that are being published today, this short monograph of Dr Laquer ranks among the best from the point of view of brevity and reliability. The author has succeeded in an admirable manner, and with rare judgment, in selecting and organizing the known facts in this important field. Hypotheses and vagaries are largely excluded. The author does not attempt, and it would be impossible in the few pages of this book, to treat in extenso the organotherapeutic aspect of the endocrine glands, the histologic aspects are also largely eliminated. It is essentially an excellent summary of the biochemical and the physiologic knowledge of the endocrine glands. As an index of the author's admirable judgment and scientific caution, a group of glands and substances are treated briefly in the last chapter under the general heading of "Hormones of Hypothetical Nature." Here the author includes the pineal body, the so-called heart hormone of Loewi, the spleen, the liver, the salivary glands and cholin. At the end of the book is an appendix which contains a bibliography of 1,200 titles arranged under the subject matter of the chapters of the book.

THE NEW YORK ACADEMY OF MEDICINE LECTURES ON MEDICINE AND SURGERY
First Series. Price, \$5. 309 pages, with 39 illustrations. New York: Paul B Hoeber, 1927.

In the preface the following statement appears, "The first series of Practical Lectures for the general practitioner arranged by the Committee on Medical Education and given at The New York Academy of Medicine in 1926-1927 met with such favor that the lectures are now published in book form in the belief that they will meet a need which is felt by the profession generally."

This series of fifteen lectures on a variety of general topics does not add anything new to medical literature, but the subjects are presented in a practical and popular style. To me the chapters on "The Treatment of Cardiovascular Syphilis" by Harlow Brooks, "General Infection by Bacteria" by Emanuel Libman, "The Cutaneous Manifestations of Syphilis" by George N MacKee, "Surgical Aspects of Diseases of the Thyroid" by Eugene H Pool, and "The Treatment of Pneumonia" by David Riesman, are of particular interest. Others may be more attracted by that on "Clinical Aspects of Common Otological Infections" by Samuel J Kopetzky, by "Remarks on Eye Conditions" by John M Wheeler, or by "Obstetrical Problems in General Practice" by J O Polak. The chapters on pathologic causes of "Human Misconduct" by Max Schlapp, "The Problems of the Child's First Year" by H B Wilcox, and "Contagious Diseases" by Shirley W Wynne are very good.

The general practitioner will doubtless find these lectures both interesting and profitable.

TRAITE DE PHYSIOLOGIE, NORMALE ET PATHOLOGIQUE Par G H ROGER, Professor of Physiologie a la Faculte de medecine de Paris, Doyen de la Faculte. Tome III. Physiologie du Foie et de L'Appareil Urinaire. Price, 85 francs. Pp 751. Tome IV. Les Secretions Internes. Price, 80 francs. Pp 858. Paris: Masson & Cie, 1928.

These two volumes maintain the elements of excellence as well as the elements of defects already pointed out in the previous volumes of this large set. The chapter on the liver by Dr Roger is on the whole excellent, so are the chapters on the kidneys by Dr Rathery and Dr DuBois.

In volume IV, dealing with the endocrine glands, the best chapters are those on the pancreas, insulin and diabetes by Dr E Hédon and Dr L Hédon, and the chapter on the hypophysis and the basal region of the brain by Dr Roussy and Dr Gournay. Dr Hédon and Dr Roussy have done valuable experimental work in their fields, and this has given tone and critical judgment to their presentation. The ovaries and testes are not treated in this volume. As an example of extreme plethora of words which in general tend to weaken many chapters of this volume, the chapter on the pineal gland by Dr Laignel-Lavastine might be referred to. The chapter runs up to nearly fifty pages and at the end the author concludes that the pineal body is really an endocrine organ, a conclusion highly problematic today. The reliable data on the physiology and pathology of the pineal gland can certainly be condensed to less than fifty pages with profit.

THE MECHANICS OF THE DIGESTIVE TRACT By WALTER C ALVAREZ, M D, Associate Professor of Medicine, University of Minnesota (Mayo Foundation). Second edition. Price, \$7.50 net. Pp 428. New York: Paul B Hoeber, 1928.

This book is intended as an introduction to gastro-enterology, but it can be read with profit by those who have worked long in this field and by all who are endeavoring to solve the problems which it presents to the physiologist or to the clinician. The second edition is practically a new book, thoroughly up-to-date. Its scope is much wider than that of its predecessor, which was devoted chiefly to the author's gradient theory. The practical application of modern physiologic discoveries is kept constantly in mind, and every effort is made to correlate them with the known clinical facts. Considerable attention is given to the alterations in function produced by disease or by operative procedures. Recent work on the gallbladder is carefully reviewed and attractively presented in the chapter on "The Mechanics of the Gallbladder." One of the most interesting portions to the internist is that devoted to flatulence, because the author has gathered together much important data regarding this common symptom.

Many readers will be pleased to find in the book pictures of numerous men who have been or are outstanding figures in the field of gastro-enterology.

The bibliography of nine hundred titles is worthy of real praise.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. TRAINING Volume 7. Price, \$3.25. Washington, D C: Government Printing Office, 1927.

The 1,200 pages of this volume do not make light reading. It is a heterogeneous hodgepodge of data which the reviewer can see no reason in the world for publishing. Nearly half of the book is made up of an appendix, in fine print, and contains documents of every conceivable character, ranging from descriptions of visits to the front by student officers, to lectures on various branches of science delivered in army training camps.

The body of the work consists of detailed plans and histories of the various training centers. Daily curriculums and courses of study follow each other, page after page, with distressing monotony.

A study of the work after the lapse of ten years since the war leaves in the reviewer's mind several queries. The first is as to the wisdom of trying to make such good soldiers out of physicians. The second is the obvious absurdity of attempting to make administrators out of all the more prominent scientists.

As a reference work for the unlucky persons who will have to organize a medical service for the next war, volume 7 will be of great value, but it does not make a very readable contribution to the present series.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY, VOLUME 12 Part 1, Physical Reconstruction and Vocational Education. Part 2, The Army Nurse Corps. Price \$3. Washington, D C: Government Printing Office, 1927.

Part 1, gives in detail the objective and methods of carrying out the physical restitution of the soldiers. Previous to the armistice an effort was made to

rehabilitate as many as possible for a return to active duty, following the armistice, to rehabilitate and when necessary to give vocational training in order that soldiers might be enabled to maintain a livelihood in civilian life. The methods by which this was attempted are given in detail.

Part 2 discusses the activities and, one might say, the hardships, especially of the overseas nurse.

UeBER EIRVEISBESCHRANKUNG IN DER BEHANDLUNG DES DIABETES GRAVIS
By KARL PETEIN, head of the Department of Medicine, University of Lund
(Sweden) and S. LANG, Karlsbad, Germany. Pp 72. Verlagsbuchhandlung
Carl Marhold, 1927.

The discovery of insulin made it necessary to publish a second edition of this book, the first appearing in 1922. Petrin uses the high fat and low protein diet, which is known as the Newburgh diet in this country. The good results are explained by Snapper's (Amsterdam) work on the secretory function of the kidney. By giving the kidney a rest from the secretion of nitrogen waste products, it is easier to take care of the beta oxidation of oxybutyric acid, diacetic acid and acetone. In this way, acidosis is prevented. Insulin, he believes, should be used only in coma and when the blood sugar does not come down to normal when the patient is on a maintenance diet.

KRANKHEITSLEHRE DER GEGENWART STROMGUNGEN UND FORSCHUNGEN IN DER
PATHOLOGIE SEIT 1914. WEISSENSCHAFTICHE FORSCHUNGSBERICHTE —
NATURWISS. REIHE, BAND XVII. By GOTTHOLD HERXHEIMER, Head of
Department of Pathology of the General Hospital of Weisbaden, Germany.
Price, 12 marks, unbound. Pp 256. Dresden: Theodor Steinkopff, 1927.

This volume is an excellent review of the new ideas and discoveries in pathology since 1914. There are good references to every subject. The author regrets that most of the references are in German, but because of the tremendous literature this was unavoidable. Over 10,000 books and papers have been reviewed. This is a valuable asset to any medical library.

DIABETIC MANUAL FOR PATIENTS. By HENRY J. JOHN. Price, \$1.75. St. Louis:
C. V. Mosby Company, 1928.

This new manual is simply and intelligently written and gives an excellent presentation of the general principles underlying the disease, diabetes, and its management from the layman's point of view, although a great deal of interesting medical statistics is included. There are numerous charts presented in attractive fashion. Of special interest are the color illustrations of the various ordinary foods, giving their composition in graphic manner. The usual diabetic recipes follow in the rear of the book as an appendix. This manual will take its place with the best of its kind in American literature. It is pleasant to notice that the author refers to the manuals already in existence as reading matter recommended for patients.

THE INTERNATIONAL MEDICAL ANNUAL. Price, \$6.00. Pp 573. New York:
William Wood & Co., 1928.

This is the forty-sixth year this book has been published, and the manner of treating the progress in medicine over the past year does not differ from the previous volumes. It summarizes very well the recent work in medicine, surgery and the specialties. References are given for more detailed data. The contributors are all English.

The book is of great value to anyone who does not find time to keep up with the medical literature, or who wishes quickly to summarize the most recent work in the treatment of disease.

XANTHOMATOSIS AND THE RETICULO- ENDOTHELIAL SYSTEM

CORRELATION OF AN UNIDENTIFIED GROUP OF CASES DESCRIBED AS
DEFECTS IN MEMBRANOUS BONES, EXOPHTHALMOS AND
DIABETES INSIPIDUS (CHRISTIAN'S SYNDROME) '

RUSSELL S ROWLAND, M D

DETROIT

CONTENTS

Introduction	
Report of Cases	
Résumé of Cases Showing Christian's Syndrome	
Christian's Syndrome and Xanthomatosis	
Historical Consideration of Xanthoma in Relation to Christian's Syndrome	
General Account of the Clinical Picture	{ Constitution General comment Symptomologic considerations Clinical and symptomologic considerations concerning syndrome
Pathologic Considerations	{ Microscopic changes Microscopic and clinical changes Microscopic changes concerning the syndrome Study of microscopic changes—conclusions
Pathogenesis in Relation to Hyper- lipidemia and the Reticulo- Endothelial System	{ Pathogenic theories Hypercholesterinemia Hyperlipidemia—clinical consideration Hypercholesterinemia and animal experimentation The reticulo-endothelial system and xanthomatosis
General Comment in Relation to the Syndrome	
Conclusions regarding pathogenesis	
Conditions that should be included as manifestations of a general disturbance of lipoid metabolism	
The nature of the nodular lesions	
Clinical features in general	
Summary and Conclusions	

INTRODUCTION

Xanthoma was first described as a rare disease of the skin. It is still classed as a dermatologic condition, although for a long time it has, in all its many forms, been considered a systemic process with lesions of the skin and tendon sheath as outward manifestations. Its common characteristics are, macroscopically, the sulphur yellow to

* From the Children's Clinic

yellow brown color of the lesions, and microscopically, the presence of large bright cells with vacuolated or "foamy" protoplasm, in consequence of a high content of a fatlike substance

In the early study, xanthoma was occasionally regarded as an inflammatory process of toxic or infectious origin, though it was more often considered neoplastic in nature. The discovery that the fatlike substance in the cells is lipoids, by Panzer, in 1906, and by Pinkus and Pick, in 1908, modified these views. Since then, xanthoma has come to be considered as a variable symptom complex resulting from a disturbance of lipid metabolism, especially of cholesterol metabolism, and related to different causes.

With the work on the reticulo-endothelial system, a new interest has been brought into the xanthoma problem. The researches on this subject indicate that all the varied manifestations of xanthoma can be brought back to the single pathologic principle that certain substances infiltrate the reticulo-endothelial system. The xanthoma cell is a cell of reticulo-endothelial origin infiltrated with lipoids. Xanthoma lesions are the hyperplastic reaction of the reticulo-endothelial system, resulting from the infiltration of lipoids in excess in the body fluids. A localization of this process produces the hyperplastic nodular lesions.

According to this interpretation, xanthoma represents the body's attempt to rid the body fluids of lipid which cannot be properly excreted and which acts as an irritant. Various lipoids (cholesterol fatty acid esters, phosphatid lipoids, possibly more complex lipoproteins) are concerned in this process, but the anisotropic ester of cholesterol has been most often observed and most studied.

This new view, though supported by animal experimentation, lacks clinical confirmation. I have had the good fortune to see two cases illustrating this condition, one case was studied at necropsy and one patient is still under clinical observation. Recent interest in reticulo-endothelial investigation makes the presentation of these cases opportune. They represent a form of xanthoma of a so-called visceral type, xanthomatosis Chalataw, in which many parts of the reticulo-endothelial system show storage of lipid or hyperplasia of lipid cells. In their consideration I shall discuss a group of cases already described by Christian and others under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus," in which the etiology is in doubt and which, I believe, represent the same condition.

The study of this series of cases in which hyperplasia of the lipid cells occurs both as a diffuse process in various organs and as localized nodular lesions clears up in a surprising way the mystery of the destruction of bone, exophthalmos, diabetes insipidus and dwarfism in the syndrome and explains the pathogenesis of a number of other well recognized clinical conditions. It also contributes a new interest to the much

discussed relationship of other reticulo-endothelial lipid metabolic conditions, notably Niemann's disease and Gaucher's disease. Xanthoma of this form is usually regarded as a rare condition, and as my cases contain so many features of clinical, as well as microscopic interest, I record them in full.

REPORT OF CASES

CASE 1—*History*—H. S., a white boy, aged 5 years and 2 months, was referred to me on Dec. 14, 1925. The father was living and well. The mother was overweight, had congenital nystagmus and was neurotic, she had not had any miscarriages. One other child, a girl, aged 2 years, was well developed and healthy. The mother's pregnancy had been normal. The birth was not difficult and had occurred at full



Fig. 1 (case 1)—Extreme exophthalmos persisting post mortem

term. At birth the infant was well developed and weighed 8 pounds (3,628.74 Gm.). He had been breast fed for fifteen months. The first teeth erupted at 6 months. At the age of 10 months, the infant weighed 26 pounds (11,799 Gm.). He had a mild facial eczema and a small abscess on the scalp at 11 months, otitis media at 12 months, and nasal diphtheria at the age of 1½ years, although it was not severe and he received antitoxin.

At the age of 2 years, following a mild attack of measles, the patient did not appear as well as usual. Six months later his tonsils and adenoids were removed. A soft swollen area was found on the back of his head at this time, which, it was thought, might have been due to a fall down some steps. As he did not complain of pain, a physician was not consulted until the child was 3 years and 9 months of age, when another swelling and soft spot appeared in the right temporal region, the mother ascribed this to his striking his head.



Fig 2 (case 1) —Lateral aspects of extensive bone defects at the vertex and base of skull and at the maxillae, Dec 15, 1925, *A*, right side, *B*, left side

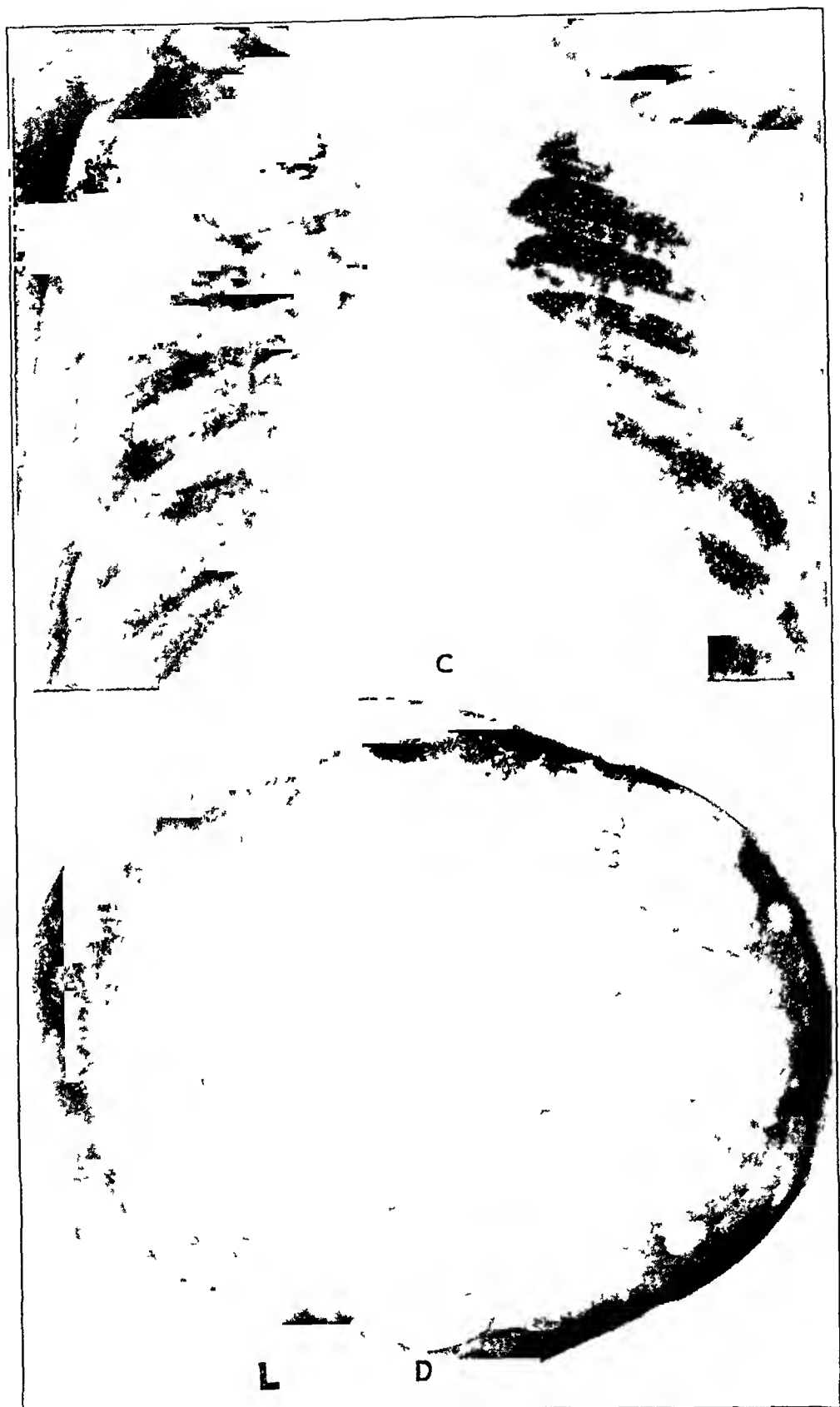


Fig 2 (case 1) —C shows extreme pulmonary fibrosis on Dec 15, 1925, D, appearance at autopsy, Jan 3, 1926, showing the character of the borders of the bone defects, some of them are sharp and discrete in outline, whereas others have a more or less moth-eaten appearance

against the corner of a table. Examination at this time showed a marked degree of exophthalmos and strabismus. The vision and eyegrounds were normal. The alveolar processes were swollen and tender, and most of the teeth were loose and infected, producing a foul odor to the breath. He had already lost a number of teeth, ten having been extracted at one time. There was a slight serous discharge from both ears, with questionable mastoid tenderness.

Roentgen-ray examination showed "multiple cranial defects involving both tables of the skull and one large defect in the occipital region of the skull where erosion of both tables was complete, suggesting a metastatic process, probably from sarcoma." The blood gave a negative Wassermann reaction. The Wassermann reaction of the spinal fluid was negative. The globulin was not increased. The colloidal gold curve was 0000000000. Neurologic symptoms were not found.

A mild pertussis developed, which made observation in a hospital impossible. The eyes, in the meantime, became more prominent, the right always more than the left, and the soft areas on the head gradually increased in size. The child did not complain of pain or headache, nor were tremor, irritability, convulsions or abnormal gait observed. His mother considered him bright, though his speech was not distinct, and it was believed that his hearing and vision were normal. His appetite and digestion were good. Abnormal urinary symptoms were not observed. He rarely wet his bed and did not show evidence of thirst or pass an unusual amount of urine. He was brought for examination because of the increasing shortness of breath and difficulty in walking, which had developed during the past three months. He had an occasional pain in the right side of the chest and a moderate dry cough and difficulty in breathing.

Physical Examination—The boy was considerably undersize for his age, he was fairly well nourished, did not show abnormal deposits of fat and was pale, cyanotic and dyspneic. He weighed 29 pounds (13.2 Kg) and was 38 inches (96 cm) tall. The temperature was 100.2 F. The respiratory rate was 32. The skin was not especially dry and did not show any eruptions. The glands in the posterior cervical region were the size of shot, other glands were not enlarged. The head was large in proportion to the body, its circumference was 50 cm. The face was oval. There was a normal amount of brown hair. A noticeable bulge was present in the frontal region, in an area 5 by 7 cm, in which there was an absence of bone. This area protruded when there was straining, as in coughing and crying, and pulsation could be felt. Most of the bony edge was sharply defined. There was a similar area in the right temporal region, 4.5 by 3.5 cm, and a smaller area in the left parietal region, irregularly outlined, 2 cm in diameter. At other points the surface was slightly elevated, as in the frontal region.

The eyes showed marked exophthalmos, greater in the right. The eye turned downward and inward. The pupils were slightly dilated, regular and equal, and reacted to light and in accommodation. The muscle response was normal and nystagmus was not present. The fundi appeared normal, the disks were well defined, and the vessels were normal in size and appearance.

There was a thin purulent discharge from both ears, more from the right. Both tympanic membranes were partially destroyed. The bridge of the nose had a sunken appearance, probably due to a bulge in the frontal region. The nasal passages were small due to evident swelling of the mucous membrane. The breath was foul. The alveolar arches were irregular and swollen and bled easily. Only three teeth remained, they were the lower incisors and were loose and covered with tartar-like substance. Tenderness and swelling were present over the maxillae, which added to the fulness of the lower portion of the face. The tongue was heavily coated a light brown. The throat was congested and a dull red,

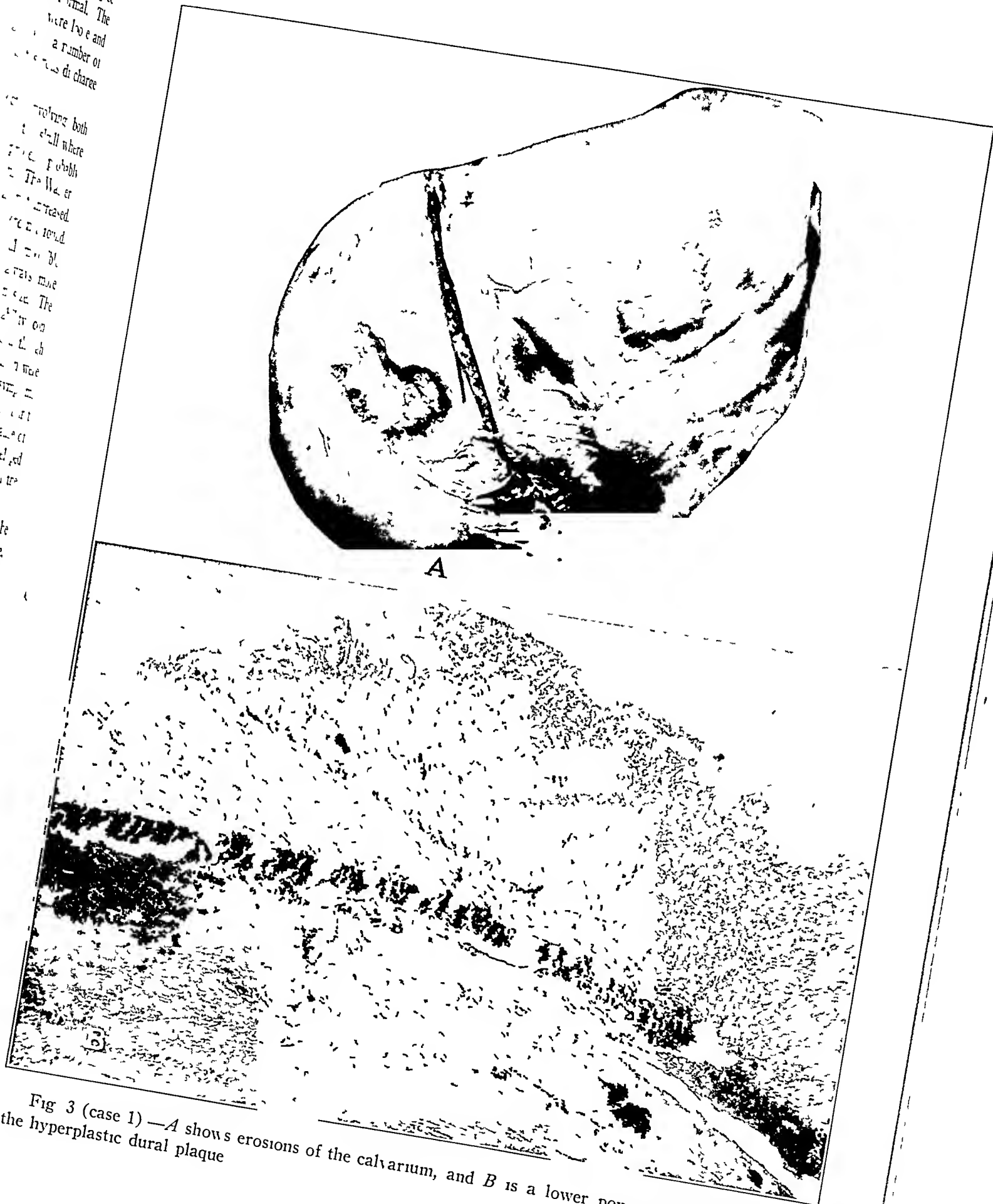


Fig 3 (case 1) — *A* shows erosions of the calvarium, and *B* is a lower power photomicrograph of the hyperplastic dural plaque

with thick purulent mucus dropping from the posterior pharynx. There was no evidence of tonsillar tissue. The thyroid was not palpable.

The heart showed a maximum impulse in the fifth space 1 cm outside the nipple line. Cardiac dullness was heard 1 cm to the right of the sternal border. The sounds were clear and distinct. Murmurs were not heard. The pulse was small and easily compressible, with a rate of 126. The blood pressure was systolic, 80, diastolic, 40. The lungs were slightly hyperresonant throughout. The breath sounds were loud and distinct, without prolongation of expiration. Occasional coarse râles were heard in both bases. The abdomen was moderately distended but not tender. The spleen was not felt, and the area was not increased to percussion. The edge of the liver was felt 3 cm below the costal margin in the mammary line. The genitals were well developed and normal. The spine showed slight prominence of the last dorsal vertebra. The muscles of the extremities were small and flabby. The hands and feet were normal in size and proportion. Clubbing of the finger tips was not present. There was slight edema of the lower extremities.

The knee reflexes were not exaggerated and were equal. The Babinski, Kernig or Brudzinski signs were not elicited. The plantar reflexes were normal.

Routine laboratory examinations showed the following. The urine was straw colored, cloudy and alkaline, with a specific gravity of 1.012, albumin, sugar and acetone were absent. The sediment showed a heavy deposit of phosphates. The Bence-Jones albumose test was negative. Examination of the blood showed hemoglobin (Dare), 57 per cent, red blood cells, 4,150,000, white blood cells, 17,350. The differential count showed polymorphonuclears, 64 per cent, large mononuclears, 32 per cent, small lymphocytes, 4 per cent. The intradermal tuberculin test was negative. The blood Wassermann reaction was negative.

Roentgen-ray Examination (Dr L. Reynolds).—On Dec 15, 1925, examination showed multiple cranial defects of both tables of the skull. "The process involves especially the frontal and parietal, as well as the occipital bones, with the greater destruction taking place in the frontal bone. The maxillae are also involved and, to a lesser extent, the mandibles. The sella turcica is distinctly visible, there being some demineralization of the dorsum sellae, but the pituitary fossa is of normal depth. The chest examination is very interesting as it reveals a diffuse bilateral fibrosis, the fibrosis simulating to a marked extent the pneumoconiosis seen in mine workers' chests. The heart is definitely enlarged, both the right and left sides participating."

Clinical Diagnosis.—The condition was diagnosed as membranous defects of the bones, exophthalmos and dwarfism. Generalized xanthoma of a so-called visceral type was found.

Course.—Dec 23, 1925. The patient had grown progressively weaker. He complained occasionally of pain in the right side. His cough was more distressing. Cyanosis and dyspnea were extreme. He was unable to sleep except when propped up in bed. He had no appetite and refused even fluids. He was almost continuously nauseated, and had vomited several times. The heart action was rapid, with a rate of 148. The pulse was small and easily compressible. No apex impulse was felt, the sounds were faint. The blood pressure was 70 systolic and 30 diastolic. Edema of the dependent parts of the body had increased. The boy was not thirsty, and passed little urine.

Laboratory Examination.—At this time, the urine was clear and alkaline, with a specific gravity of 1.012. Albumin, sugar, acetone and diacetic acid were absent. Microscopic examination gave negative results, except for an excess of phosphates.

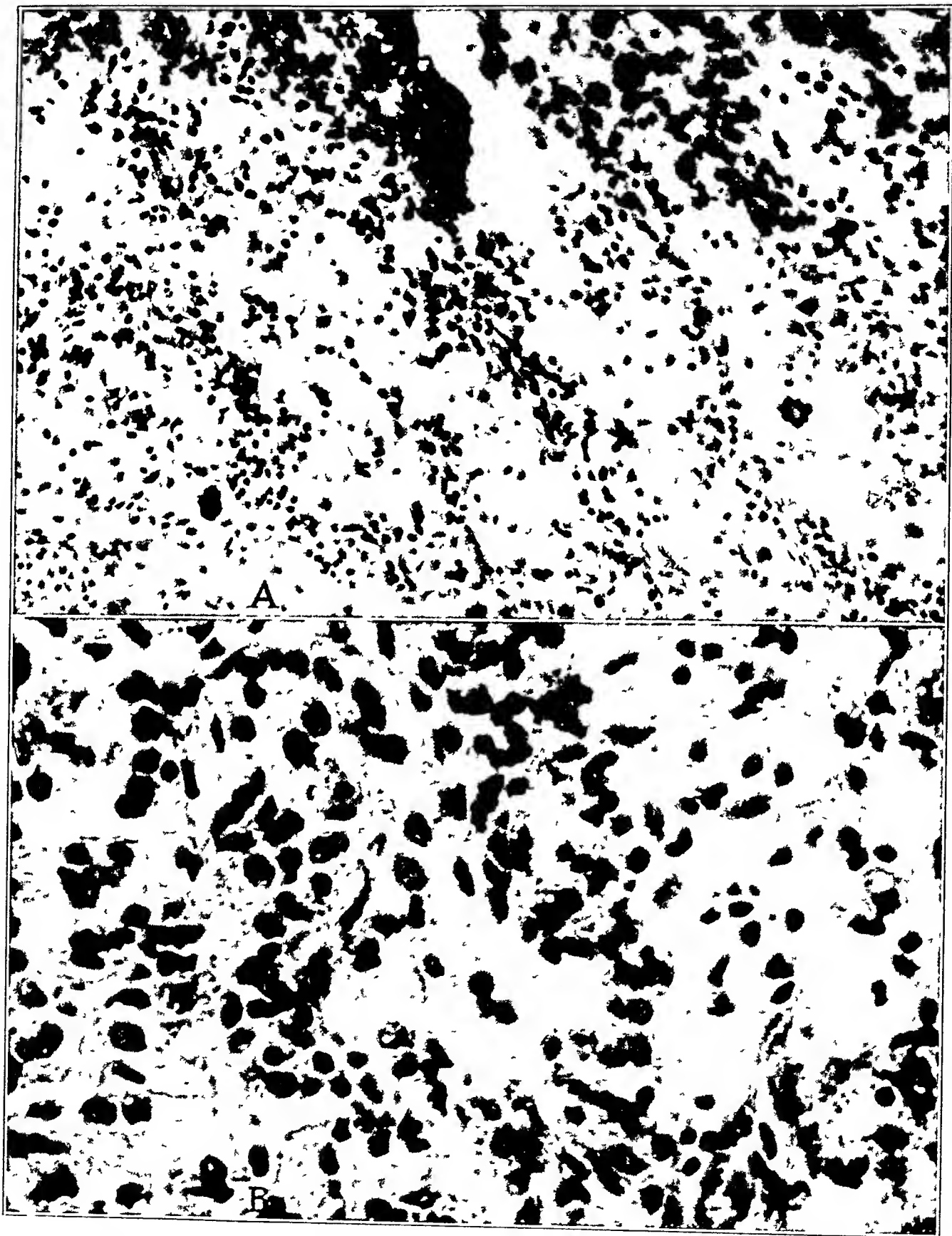


Fig 4 (case 1) —*A* shows lipid (foam) cells and foreign body giant cells in dural plaques, low power, *B*, lipid (foam) cells and foreign body giant cells in dural plaque, higher magnification

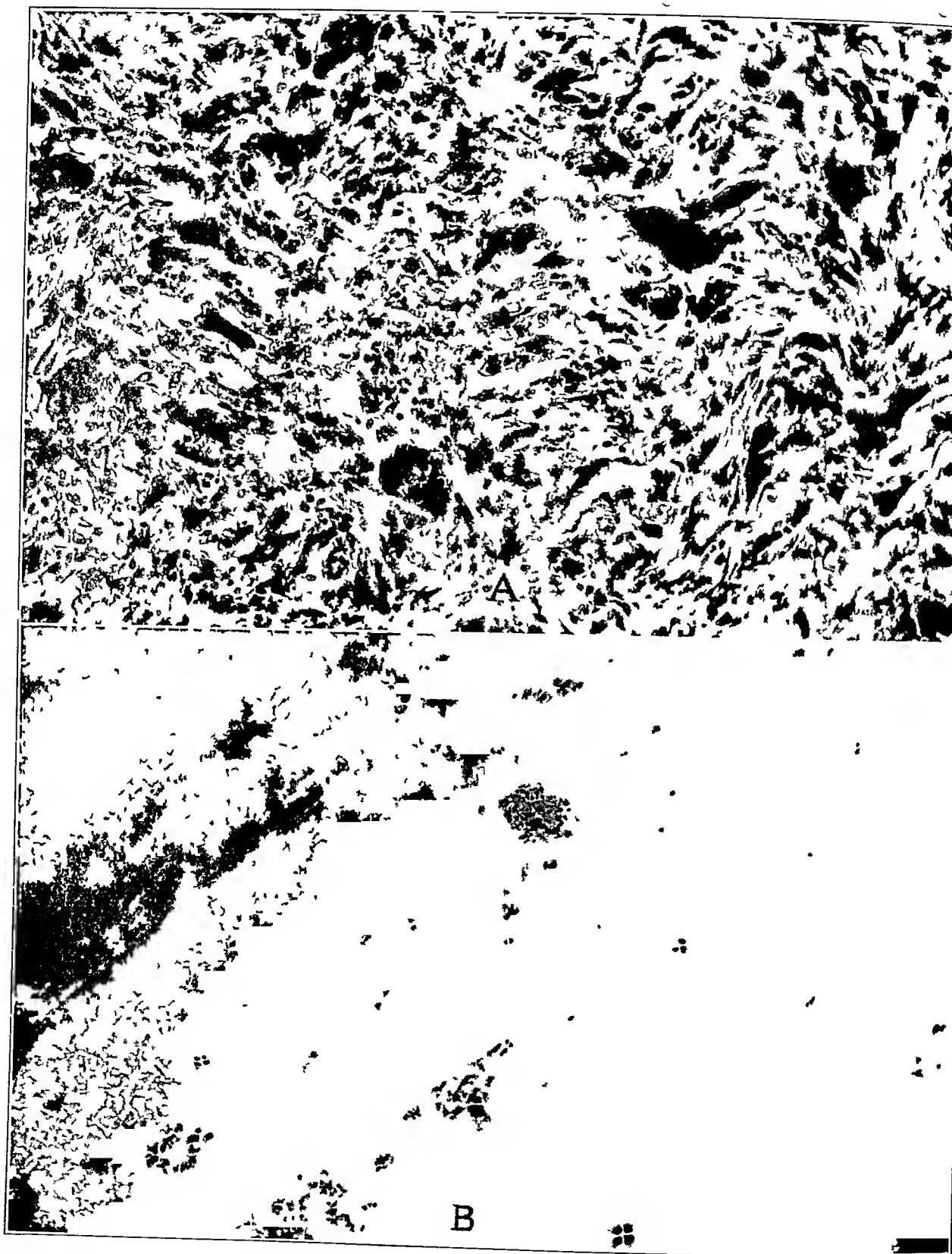


Fig 5 (case 1) —*A*, dural plaque stained with sudan III, showing large amount of fat, *B*, section of dural plaque showing anisotropic fat as it appears in the polarizing microscope

The blood showed hemoglobin (Sahli), 64 per cent, red blood cells, 4,560,000, and white blood cells, 17,600. The differential count showed polymorphonuclears, 73 per cent, large mononuclears, 20 per cent, and small lymphocytes, 7 per cent.

The patient was removed to Harper Hospital, Jan 1, 1926, where he failed rapidly and died the following morning. The fatal termination was attributed to cardiac failure due to impaired circulation resulting from the extensive pulmonary fibrosis.

Autopsy Report (Dr P F Morse, Jan 3, 1926) —There was extreme pallor of the skin and marked exophthalmos of the type seen in cavernous sinus thrombosis. The fingers, toes and lips were markedly cyanosed. There was a serous discharge from both ears. Palpation of the skull revealed many cranial defects in which the bone appeared to be missing.

When the head was opened, the scalp was found normal in appearance. When the calvarium was exposed, there were numerous annular defects of the cranial bones which varied in size from 0.75 to 4 or 5 cm in diameter. These defects had slightly wavy edges, but were fairly sharp. The bone at the margin was firmer than normal and the defect itself was filled with a gummy, semicaseous bright yellow tissue of rubbery consistency. The tissue appeared to be uniform in structure and on section presented the same appearance that it did externally. When the skull cap was removed, it was found that the tissue was easily pushed out of these defects, leaving a somewhat ragged hole in the skull. This tissue appeared to arise from and be continuous with the dura and to give the impression of a peculiar form of granulomatous tissue arising from the dura and invading the skull. The brain was somewhat edematous. The dura stripped easily from its superior surface. When the brain was removed, a gross lesion of the brain substance or ventricular system was not discovered. When the base of the skull was inspected, it was found irregularly covered over with these yellowish, granulomatous swellings which had destroyed a large portion of the bone of the base, extending forward into both orbits and completely surrounding the region of the hypophysis and destroying the sella turcica. The nasal sinuses showed nothing of note. When the temporal bone was opened, the tympanic membranes were found destroyed, and there was a marked atrophic inflammatory process of both middle ears without destruction of the bone.

When the body cavities were opened in the usual manner, the sternum appeared normal with a normal marrow content. The heart was markedly enlarged and dilated, both right and left. When the heart was removed, there was a moderate hypertrophy of the muscle of both ventricles and relative dilatation of the tricuspid and mitral rings, but no other cardiac lesion. The first portion of the aorta and coronary vessels appeared normal. The lungs were voluminous and felt fibrous to palpation. The left lung was somewhat adherent over the posterior lateral aspect of the costal pleura, the adhesions being of the same peculiar yellowish, gummy nature that was noted in the granulomas of the skull. When the lungs were removed, they were found distended and firm to the touch and on section presented a remarkable appearance. The whole lung was a mass of communicating vesicular cavities. These cavities varied in size from that of a pin head to that of a large pea. The septums between the cavities were fibrous and inelastic. The walls of the blood vessels were somewhat thickened. The general appearance suggested a low grade pulmonary hypoplasia, or an intense or diffuse form of pneumonitis with marked emphysema.

When the abdomen was inspected, the liver was found to be about normal in size. When it was sectioned, it did not present a remarkable appearance. The spleen was normal. Both kidneys were normal in size and on section presented a

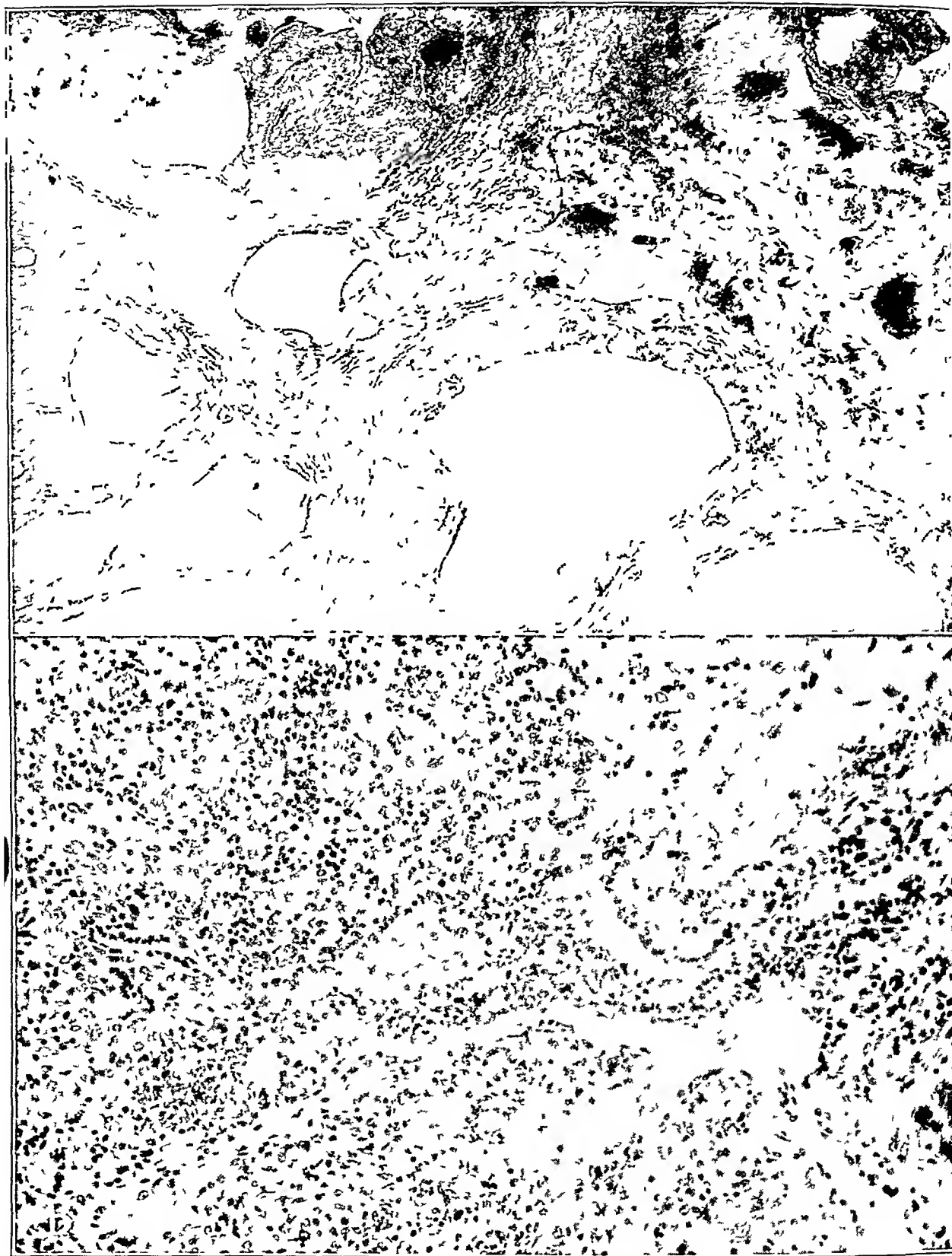


Fig 6 (case 1) — *A* shows chronic bronchopneumonia with patches of fibrosis and alternating patches of emphysema, *B*, chronic bronchopneumonia with localized patches of fibrosis

normal relation of the cortex to the medulla. The capsule stripped easily. The gastro-intestinal tract, including the pancreas, did not present gross pathologic changes. The pelvic organs were normal. When the ilia were exposed there was found in the cavity of the right ilium a yellowish plaque about 1 cm in diameter with a bone defect of the same character as that seen in the skull. A similar yellow plaque 2 cm in diameter protruded from the periosteum on the right side of the body of the first lumbar vertebra.

"Roentgen-ray study made of the skull cap at the time of the autopsy reveals in a striking way the cranial defects that were observed in the x-ray study of the skull during life. Some of the defects show a very sharp discrete outline of their

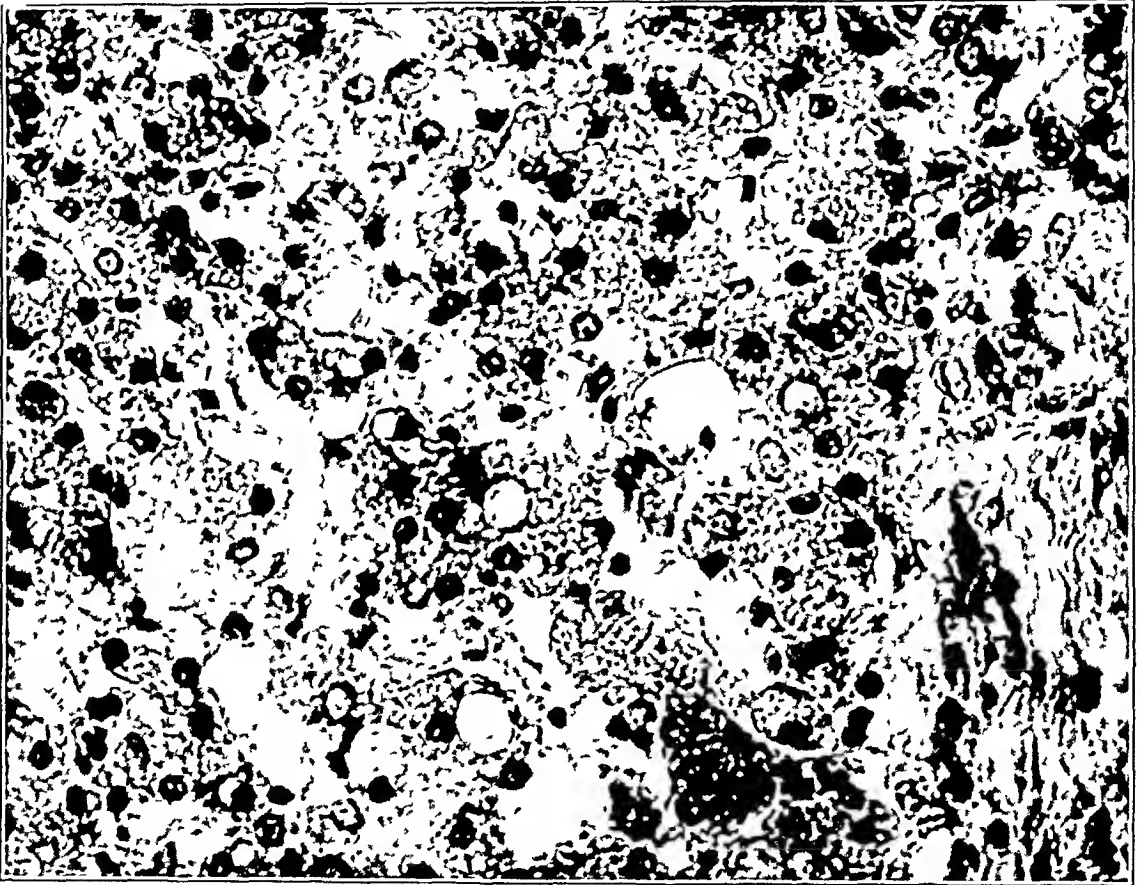


Fig 7 (case 1) —Photomicrographic appearance of liver showing slight lipoidosis of the liver cells with marked lipoidosis of the Kupffer cells

'bony borders,' whereas others have a more or less moth eaten appearance. This is especially true of the frontal bone on the right side" (Dr L Reynolds)

Pathologic Report (Dr A S Warthin) —The thyroid gland showed a colloid content normal for this age, with undeveloped adenomatous tissue. Throughout the gland, there were a number of sharply circumscribed areas of proliferation of the stroma having an epithelial appearance in the center with some lipoidosis.

The suprarenals showed hypoplasia which was especially marked in the medulla. Moderate lipoidosis of the cortical cells was present. In the perisuprarenal tissue there were small areas of proliferating reticulo-endothelium. The large epithelioid cells showed more lipoidosis and some pigmentation, thus resembling xanthoma cells. In one section in the medulla were small areas of proliferating reticulo-endothelial cells with lymphocytic infiltration.

The lymph nodes showed lymphoid exhaustion of the germ centers. Proliferation of the reticulo-endothelium with lipoidosis and slight pigmentation was present. The proliferation of the reticulo-endothelium and lipoidosis varied greatly in the different nodes, being quite marked in some, while others showed them to a slight degree. All through the retroperitoneal tissue there were bands and strands of this atypical tissue.

The kidneys were congested with edema and some lipoidosis of the renal epithelium. Small concretions of lime salt were found in some of the tubules. Proliferation of the reticulo-endothelium and lipoidosis were not found.

Sections from the brain did not show any pathologic change except slight edema.

The liver presented marked passive congestion. There was slight lipoidosis of the liver cells, more marked in the periphery of the lobules, and some atrophy of the cells. Many lipid Kupffer cells were found.

Chronic bronchopneumonia, with localized patches of fibrosis and alternating patches of emphysema, was found in the lungs. The reticulo-endothelial cells around the pulmonary vessels showed the same hyperplasia and lipoidosis seen elsewhere, and projecting into the larger bronchi were papillary overgrowths of fibroblastic tissue and reticulo-endothelial tissue showing lipoidosis. The pleura was thickened with reticulo-endothelial hyperplasia and lipoidosis.

The muscle fibers of the heart were fairly well developed for this age. Little lipoidosis of the muscle and no reticulo-endothelial proliferation and no lipoidosis in the stroma were found. The testes were apparently normal for the age. Lipoid cells were not found in the testes or epididymis.

The pineal gland was edematous and congested. Lime salt deposits or lipoid cells were not present.

The bones showed atypical marrow. There was reticulo-endothelial hyperplasia with many multinuclear giant cells and many lipid cells. Rarefaction of the bony trabeculae was found. (The bone absorption resembled that seen in some cases of osteomalacia.)

The dural plaques consisted of masses of lipid-containing cells of reticulo-endothelial type resembling xanthoma. Throughout were numerous multinuclear giant cells. In old tissue of the dura were numerous small calcareous concretions. In lipid masses were areas of cholesterol crystal formation, with cholesterol clefts and with many multinuclear giant cells. Giant cells, evidently foreign body giant cells, surrounded the cholesterol crystals. These plaques did not suggest infectious granuloma but resembled xanthoma or masses of cells of the xanthoma type, and probably consisted of proliferated reticulo-endothelial cells with cholesterolosis. Fat stain showed cells to be loaded with lipoids.

CASE 2—History—R. R., a white boy, aged 3 years and 11 months, was referred for further study from the clinic of the Children's Hospital of Michigan, Feb. 14, 1926.

The parents were living and well. They had three other children, aged 11, 9 and 7 years, respectively. The oldest, a boy, had rheumatism and chronic cardiac disease. The maternal grandmother was operated on for cancer of the breast when she was 50. The maternal grandfather suffered from kidney stone. The paternal great grandfather died with diabetes mellitus. The family history did not show evidence of tuberculosis, syphilis, asthma or renal disease. There was no further history of cardiac disease, diabetes or malignant disease.

Both the pregnancy and the birth had been normal. The patient had been a "fine strong baby," weighing $8\frac{3}{4}$ pounds (3,968.94 Gm.). He had been breast fed for four weeks, and then was given a mixture of cow's milk, milk sugar and lime

water. He did not receive cereals or cod liver oil, but was given orange juice from the age of 3 months on, and vegetables and broth during the latter part of the first year. After the first three months, he developed rapidly, had teeth at 6 months, stood with support at 8 months and walked at 14 months. He did not catch cold easily or have sore throat. There were no illnesses during the first year. He had a moderately severe attack of pertussis when he was $1\frac{1}{2}$ years old.

When he was a little under 2 years, he became irritable, complained of a sore mouth, began to ask for water frequently and to pass large amounts of urine

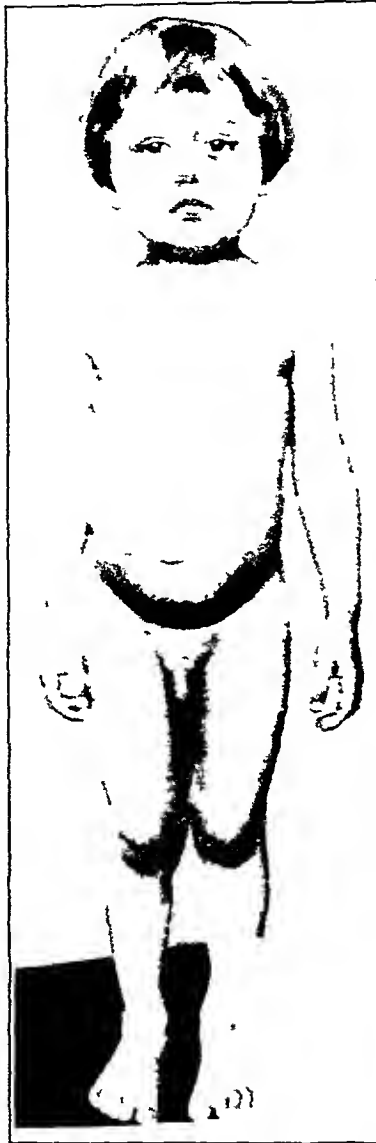


Fig 8 (case 2) —Left exophthalmos, normal proportions of body

His mother ascribed these symptoms to teething. When 22 months old, he was standing in a rocking chair and tipped over sidewise striking his head. For three or four days following this, he was drowsy, irritable, complained of pain and slept a good deal. The soreness of the mouth grew worse, and several of the teeth loosened and came out. At 26 months he had a second fall, after which considerable swelling appeared over the frontal bone. This was again followed by drowsiness and some stupor. About this time he had suppurative otitis media on the left side. The symptoms of thirst and frequent urination were variable. His mother stated that if he were allowed to drink at the tap he would some-

times fill himself until he complained of pain and finally vomited clear water. She estimated that he passed from 6 to 8 quarts (5,678 to 7,570 cc) of urine daily and that he asked for a drink of water every hour. When 2 years and 6 months old, on Sept. 12, 1924, he was admitted to the Children's Hospital of Michigan. Examination showed a well nourished boy, who did not appear sick but who was irritable and fussy. In the left parietal region a cranial defect the size of a nickel was noted, also small palpable glands involving the posterior cervical chain. His abdomen was slightly distended. The rest of the physical examination gave negative results.

Laboratory and Special Examinations (from the Children's Hospital record) — The urine was clear and alkaline, with a specific gravity of from 1.000 to 1.003,



Fig. 9 (case 2) —Left exophthalmos

albumin and sugar were not present. The Bence-Jones albumose test was negative on repeated examinations. Microscopic examination gave negative results. Examination of the blood showed red blood cells, 3,850,000, white blood cells, 9,800. The differential count showed polymorphonuclears, 71 per cent, large mononuclears, 3 per cent, small lymphocytes, 26 per cent. The urea nitrogen was 16 mg per hundred cubic centimeters. The blood sugar was 60 mg per hundred cubic centimeters. The blood Wassermann reaction was negative. Two dextrose tolerance tests showed blood sugar well within normal limits. The amount of urine was not increased by the test, nor did the sugar appear in the urine. The response to pituitary was pronounced at first, but the dosage had to be increased and was discontinued before the patient left the hospital, because the therapeutic effect was not satisfactory. The Pirquet test was negative. The

cerebrospinal fluid was clear and came under normal pressure. The cell count was 8 per centimeter, the globulin and the spinal fluid Wassermann tests were negative.

X-ray Examination—A report on Sept 16, 1924, stated "The skull shows evidence of multiple cranial defects. One large defect involves the entire base of the skull and fronto-temporal region on the right side. The process has entirely destroyed the floor of the sella, only the anterior clinoid processes and dorsum sella remain as landmarks. A large defect also appears in the left parietal region near the vertex of the skull with a smaller one in the vertex. There is evidence of involvement of the fifth rib on the right side in the posterior axillary region. No involvement of the long bones, but an area of decreased density in the right ilium."

During the patient's stay of more than two months in the hospital, his temperature ranged from 97.6 to 99.7 F, with an occasional unexplained elevation as high as 101. For about a week, there was moderate elevation of temperature, resulting from a small abscess in the right buttock which was opened and drained. A rise also occurred following resection of a portion of the fifth rib which, according to the x-ray reports, showed changes similar to those in the skull. A specimen was taken for microscopic examination, but a report was not made. The pulse rate varied from 110 to 140, and the respirations, from 24 to 30 a minute. The weight fluctuated considerably with variations in fluid intake and output, but it was 23 pounds and 7 ounces (10,631 Gm) on admission and 21 pounds and 14 ounces (9,922 Gm) on discharge.

The following possibilities were considered in the diagnosis at this time: "Lytic destructive process, sarcoma or myeloma. Patient discharged Nov 20, 1924, unimproved, to return when the condition became more serious."

When I first saw him, on Feb 14, 1926, fifteen months after he left the hospital, the patient had not had any acute illnesses. His appetite and digestion were good. He complained of only moderate thirst and passed from 6 to 8 quarts of urine in twenty-four hours. His mother had noticed that he had not grown like her other children. Besides polyuria and polydipsia, his chief complaint was sore mouth. His mother had not noticed the fact that the left eye protruded more than the right eye, but she said that the soft spot on the head had increased in size. There had not been any complaints of headache, digestive upset, visual disorder, diplopia, vertigo, fainting spells or convulsions. The mother thought that the hearing was acute and the mental state normal.

Physical Examination—The boy appeared fairly well, and was not in pain or distress, though he was irritable and fussy. The nutrition and color were fairly good. The skeletal proportions were normal, though small for his age. He weighed 28 pounds (12,690.5 Gm), and was 35 inches (88.9 cm) tall. The temperature was 99, pulse rate, 116, and respirations, 26. The skin was clear, elastic and dry, without any eruptions. The panniculus was well developed, without abnormal deposits of fat. The glands were not enlarged. The head was symmetrical and square in type, with a normal amount of light brown hair. On palpation, an irregular oblong defect was felt in the skull in the left parietal region near the vertex, 3 by 4 cm. The edges were sharply defined. There was little, if any, tenderness on pressure. The left eye was slightly more prominent than the right. The pupils were equal and regular and reacted to light and in accommodation, the sclerae were blue, photophobia, diplopia, nystagmus, or palsies of the extrinsic eye muscles were not present. Von Graefe's sign was not present. The fundi appeared normal. The ears were normal. The nose was small, its

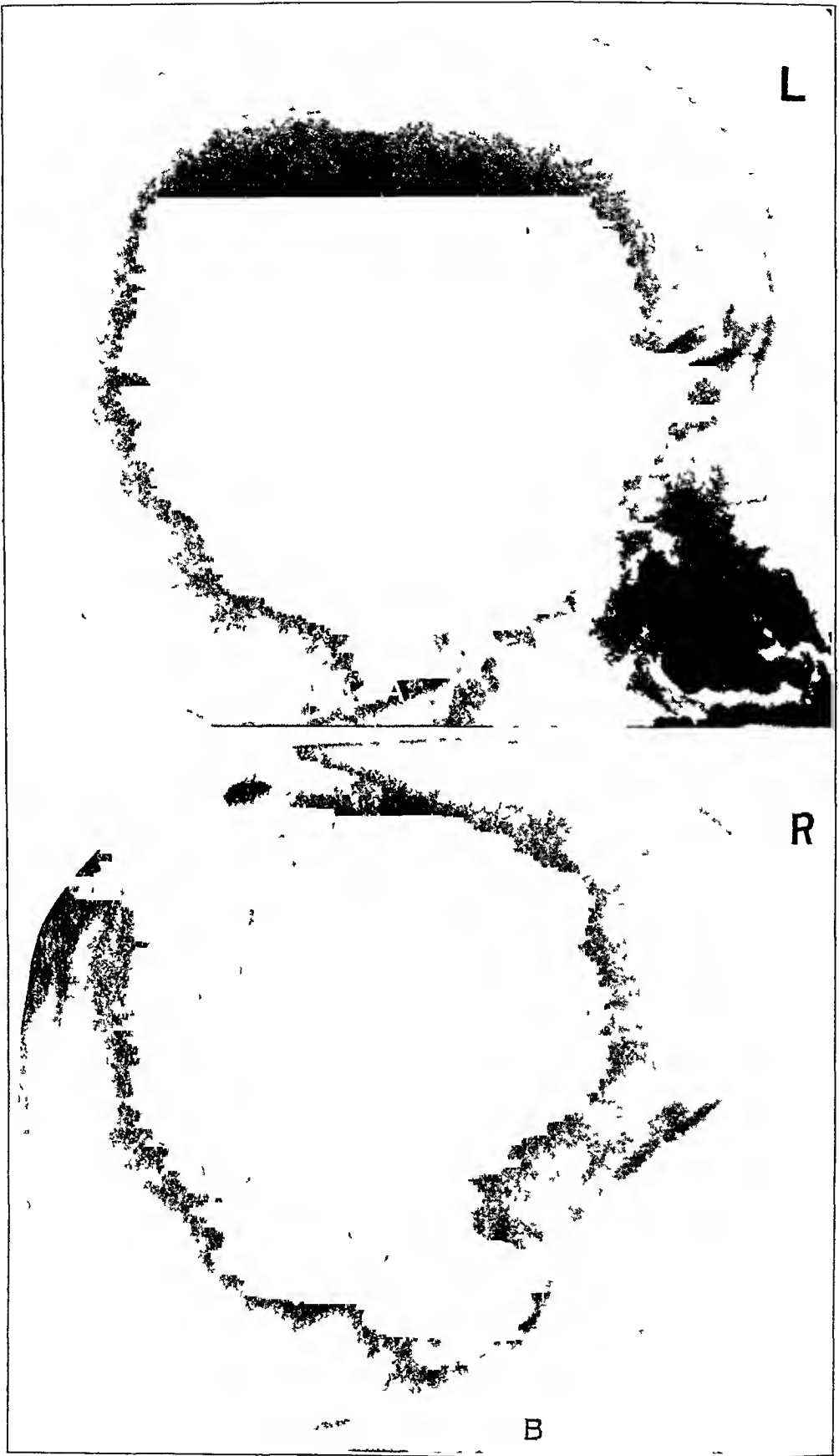


Fig 10 (case 2) —*A* shows bone defect in parietal region and extensive defect at base of skull, Sept 16, 1924, as compared with *A*, *B* shows a gradual increase in the bone destructive process at the vertex and base of skull and in the maxillae, Nov 1, 1924



Fig 10 (case 2) —On Feb 20, 1926 the lateral aspects show that the bone defects at the vertex and base of skull are much more extensive than on examination seventeen months before, *C*, right side, and *D*, left

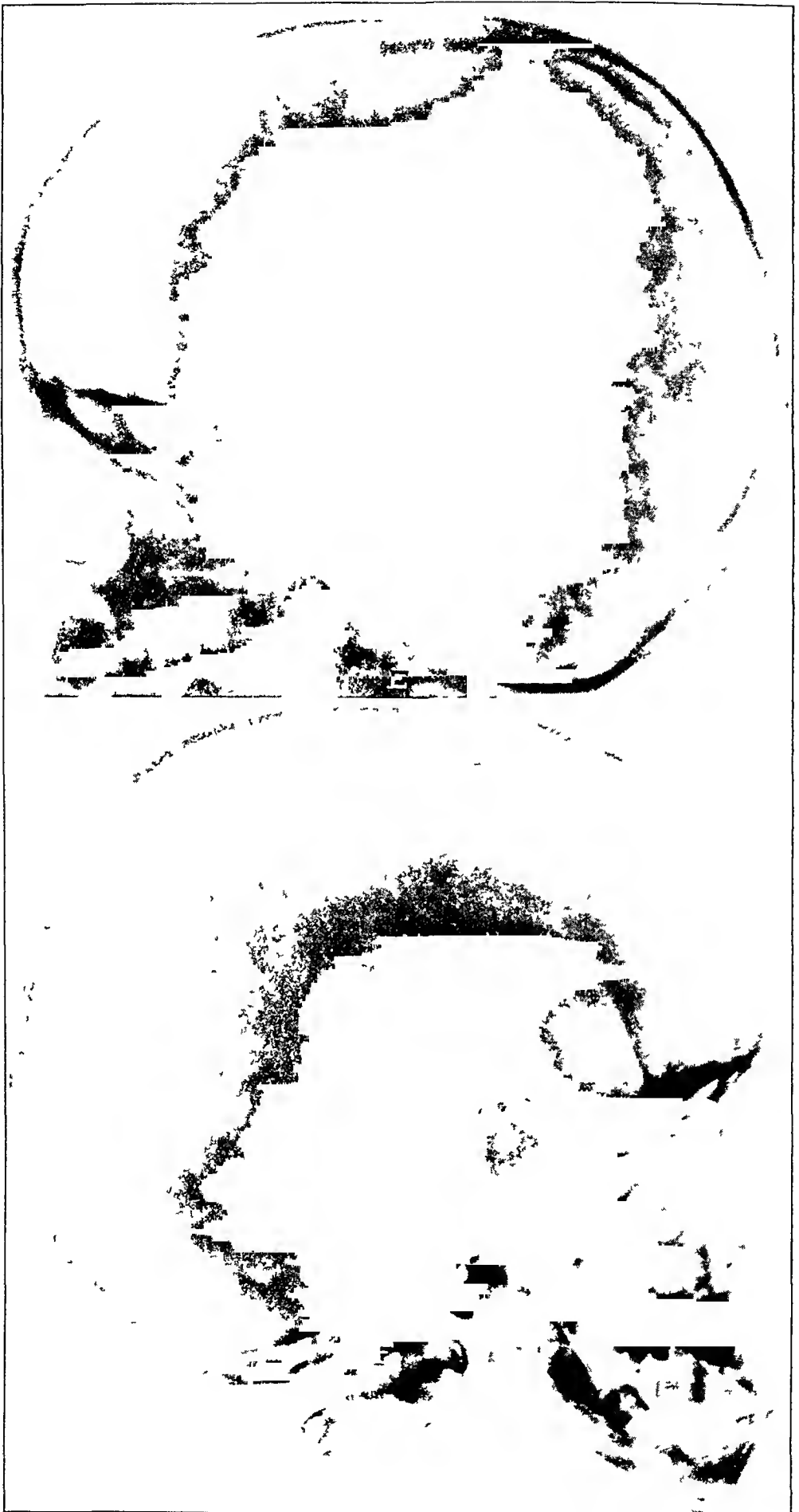


Fig 10 (case 2)—*E* shows, on Oct 27, 1927, the remarkable regeneration of bone in the areas which showed progressive bone destruction twenty months before, *F* shows the remarkable degree of bone regeneration on Nov 27, 1927, twenty months after examination in *D*

passages were narrow, the mucous membranes were swollen, and there was a slight nasal discharge. The mouth was small, the gums were swollen and tender, bled easily and were retracted from the teeth. All the molar teeth in both the upper and the lower jaw were loose. The teeth appeared normal. Pus could be expressed about some of them. The tongue protruded in the median line without tremor. The tonsils were moderately enlarged and with the pharynx were congested. The voice was of good quality. The neck did not show abnormal pulsations. The thyroid was not palpable. The heart showed an apex impulse in the fifth space just inside the nipple line. The action was regular, the sounds of good quality, and no murmurs were present. The lungs showed good resonance, and normal breath sounds were heard throughout. The abdomen was moderately distended but not tender. The spleen was not felt. The edge of the liver was palpable below the costal margin in the nipple line. The superficial and deep reflexes of the extremities were all normal. The genitals were normally developed.

Roentgen-Ray Examination (Dr L. Reynolds).—On Feb. 20, 1926, roentgen-ray examination revealed "Marked extension of the bone erosion which has involved the right and left parietal bones. The process has extended posteriorly and now involves the temporal bones on both sides, continuing on the right side as far as the occipital bone in the region of the lateral sinus. There is definite involvement and destruction of the mastoid cells, excepting one or two cells seen in the region of the antra which are still pneumatic. In the film taken in the postero-anterior plane one is able to note the rather extensive process which has involved the supra-orbital plate on both sides, this process being more extensive on the right side, where there is very definite involvement of the frontal bone and extension into the superior and lateral orbital ridges. The maxillae are also involved. There is erosion of the lateral wall of the left maxilla and clouding of the antrum. The chest examination reveals evidence of repair of bony structure in the shaft of the fifth rib in the posterior axillary line, at the point where specimen was removed for biopsy. However, there has been an extension of the process anteriorly in the shaft of the fifth rib. None of the other ribs are seen to be involved and all the long bones are normal in appearance."

A determination of the blood serum cholesterol at this time gave a value of 315 mg. per hundred cubic centimeters (Myer-Wardell method).

Clinical Diagnosis.—The condition was diagnosed as membranous bone defects, exophthalmos, diabetes insipidus, and generalized xanthoma of a visceral type.

Laboratory Study and Special Examinations.—On April 18, 1926, the patient was admitted to Harper Hospital. In general these examinations corresponded to those previously made. The urine was amber, acid and negative for albumin and sugar, with a specific gravity of 1.000 to 1.004. It varied in daily amount from 5,000 to 6,000 cc. Under the administration of sodium chloride, there was little tendency to concentration, and the sodium chloride was readily excreted. The Mosenthal test demonstrated the large increase in excretion of water and that the amounts excreted during the day and night were in normal relation. The excretion of chloride and nitrogen was within normal limits. Solution of pituitary given by mouth had no effect, but obstetric pituitary solution given hypodermically reduced the amount of urine to normal and did not materially affect the specific gravity. The dextrose tolerance test showed: fasting, 0.087 per cent, one hour, 0.117 per cent, three hours, 0.083 per cent. The urine was not increased, and sugar did not appear in the urine. Examination of the blood showed: hemoglobin (Sahli), 68 per cent, erythrocytes, 5,600,000, leukocytes, 13,500. The differential count showed: polymorphonuclears, 67 per cent, large mononuclears, 7 per cent, small lymphocytes, 24 per cent, and eosinophils, 2 per cent. Six separate exami-



Fig 11 (case 2) —*A* shows erosion in fifth rib on the right side, on Nov 6, 1926, *B* almost complete healing, on Nov 27, 1927, of erosion in fifth rib on right side with formation of callus where specimen for biopsy was taken

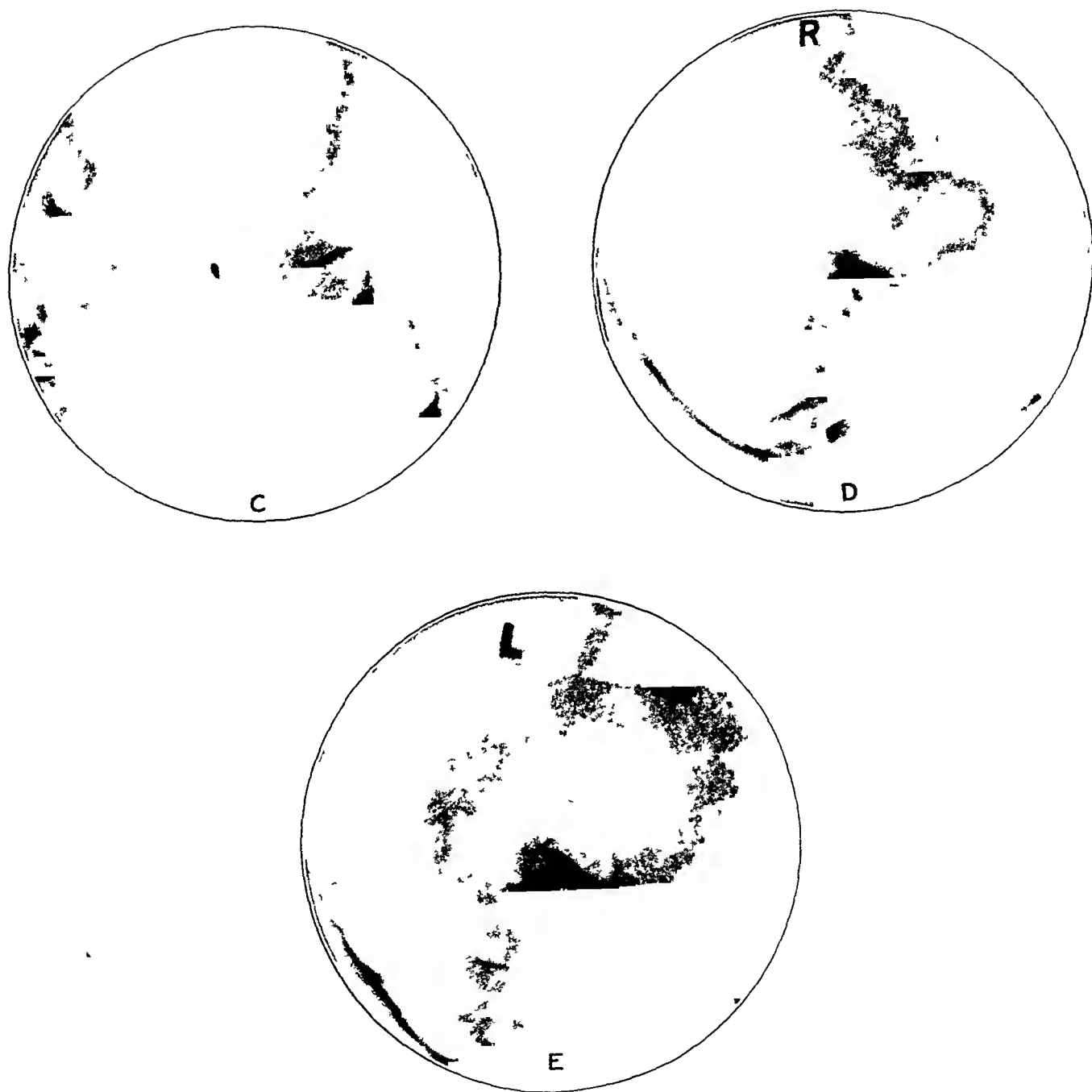


Fig 11 (case 2) —C shows extensive bone destruction about the orbits, especially marked on the left side, on April 26, D, extensive destruction involving the right mastoid, on April 26, E, extensive bone destruction involving the left mastoid and base of skull, on April 26

nations of blood cultures gave negative results, one showed contamination, and two anaerobic cultures were negative. Blood chemical determinations showed nitrogen, 23 mg, sugar, 60 mg, calcium, 9 mg, uric acid, 4 mg, cholesterol, 256 mg, fatty acids, 400 mg, all per hundred cubic centimeters of blood serum. The spinal fluid showed cell count, 8, globulin, negative, colloidal gold, 000000000, Wassermann, negative, cultures from the fluid did not show growth, and injection into guinea-pigs gave negative results. Intradermal tuberculin tests were negative. Basal metabolism tests were attempted but were considered unsatisfactory. Pharmacologic tests, in which varying doses of anterior lobe pituitary and obstetric pituitary solution hypodermically were used, did not give an unusual reaction that could not be regarded as normal, suggesting that a disturbance of pituitary function had not occurred.

Growth Characteristics (Dr C J Marinus) —On April 22, 1926, examination showed "The face is definitely square in type, some flattening of the nose, small mouth, eyes slightly suggestive of mongol type. Skin definitely dry. Hands and feet good size and proportion. Measurements: Circumference of head around forehead, 19 inches, vertical across the jaws, 20 inches, largest circumference, 21 inches. Neck, $9\frac{1}{2}$ inches, shoulders, $20\frac{1}{2}$ inches, chest, 20 inches, abdomen, 19 inches. Span, $34\frac{1}{2}$ inches, sitting height, $19\frac{1}{2}$ inches, lower half, $16\frac{1}{2}$ inches, upper arm, $9\frac{1}{2}$ inches, lower arm, $10\frac{1}{2}$ inches, thigh, $10\frac{1}{2}$ inches, leg, 10 inches. These measurements are normal, the height being slightly greater than the span, and the lower half somewhat less than the upper half. There is no evidence of insufficiency of anterior lobe of pituitary as shown by bone development. There is no deficiency of posterior lobe as shown by lack of fat changes. The dryness of the skin is that usually seen in diabetes insipidus due to disturbed water balances rather than that due to thyroid insufficiency. At the present time this patient does not show any developmental changes characteristic of pituitary disease. There is a moderate dwarfism which is, however, not characteristic in type. The signs, by which I am accustomed to diagnose pituitary insufficiency, do not usually appear before the age of 8. This case is of particular interest, because the x-ray examination presents positive evidence of pituitary damage and because of the diabetes insipidus. The proportions, in anterior lobe deficiency, tend to resemble those of infancy, so that in a patient of this age it is impossible to say whether the decrease in height is due to pituitary insufficiency or falls in the class of true dwarfism."

Ophthalmologic Examination (Dr Parker Heath) —On April 24, 1926, examination showed "Vision in each eye, as determined by objects, is normal for distance and near. Convergent power normal, no paralysis of extrinsic muscles. Pupils equal in diameter and react promptly to light and in accommodation, consensual reflexes are present. The left eye is slightly more prominent than the right, being proptosed approximately 2 mm. There is none of the lid lag sign found in exophthalmic goiter. Neither globe is congested. Ophthalmoscopic examination of the right eye: pupil dilates evenly, media clear, disk normal in color, rings slightly blurred, vessels normal in caliber and course, foveal reflexes present. The left eye is essentially the same. The mechanism of the exophthalmos, judging from x-ray plates, may be due to letting go of the apex of the orbit, as suggested by a previous observer."

Roentgen-ray Report (Dr L Reynolds) —On Oct 27, 1927, the report stated "At this time there has been a striking change. The previously noted large cranial defects show complete bony degeneration, except for a very small discrete area in the left parietal bone, where a large defect was formally observed. One is able to make out only the faintest cranial defect and this is limited to the inner

table The very large defects noted in the region of the anterior and middle fossa on the right and left sides show complete regeneration There has been, however, no attempt at repair of the sella turcica, although the supra-orbital plates show distinct bony repair The pelvis and long bones reveal no evidence of abnormality, and at no time has there been any destruction of the long bones, other than the shaft of the fifth rib on the right side"

Course—On Nov 8, 1927, the patient appeared well, was lively and had a good color Measurements showed that he had gained $3\frac{1}{2}$ inches (88 cm) in height during the past year The exophthalmos had noticeably receded The soft spot in the left parietal region was markedly reduced in size, so that it could be located only with difficulty The sinuses and teeth were in good condition The boy rarely asked for water and passed less than 3 quarts (2,839 cc) of urine during the day and about half this amount at night, in comparison with twice that much a year ago A determination of cholesterol showed 111 mg per hundred cubic centimeters of blood serum

RÉSUMÉ OF CASES SHOWING CHRISTIAN'S SYNDROME

In 1919, H A Christian, under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus—an unusual Syndrome of Dyspituitarism," reported a case presenting this syndrome and cited two similar cases previously described by Schuller Since then Hand has recorded three cases, including one of Kay's Grosh and Stiffel, Thompson, Keegan and Dunn, Danzer, and Kyrklund have each reported one case

The syndrome is so striking and the symptomatology so similar that there can be no doubt of their representing the same disease as that in the two cases I have just described

Christian's patient, a girl, aged 5 years, was normal and healthy until 3 years of age At this time her teeth became loose and her gums swollen and tender She had never been ill, except that she had mumps three or four months previously When she was $3\frac{1}{2}$ years old she developed thirst and polyuria, and the right eye became prominent Examination at 5 years showed defects in the bones of the skull, exophthalmos, loose teeth with swollen gums, some of the teeth missing, and typical diabetes insipidus The Wassermann and tuberculin tests were negative Neurologic symptoms were not present Christian considered the condition as probably due to disturbed pituitary function

Schuller's first patient, a boy aged 16 years, had a severe fall on the abdomen at the age of 6 years Following this accident he suffered nocturia His growth was retarded and he later developed the picture of dystrophia adiposogenitalis When he was 12 years old, a discharge began from his left ear Exophthalmos was first observed at the age of 15 years Examination showed extensive cranial defects On both sides of the neck above the clavicle were "fatty tumors" Schuller ascribed the condition to a tumor at the base of the brain, an angioma of either the dura or skull bone

Schuller's second patient, a girl of 4 years, was normal up to the age of $1\frac{1}{2}$ years, when she had whooping cough When 2 years old she developed thirst and polyuria, and exophthalmos was first noted She was under observation for a number of years, during which time there was some retrogression in the defects of the skull The diagnosis was "anomaly of the skeleton resulting from disease of the hypophysis"

Hand's first patient was a boy, aged 3 years, who complained of thirst and polyuria, which had begun eight weeks previously He had enterocolitis at 5 months and measles and croup at 2 years The child was undersized and poorly

nourished, with light brown hair and bronzed dry skin. The skin of the abdomen was covered with petechiae and "an eruption something like scabies." Later these spots increased in number and were elevated, appearing over the body and extremities. His eyes were in a condition of exophthalmos, giving him a "frog-like" appearance. Polyuria and polydipsia were pronounced. At autopsy, when the scalp was removed, a yellow nodule the size of a five cent piece was noticed near the right parietal eminence. When the skull cap was removed, this nodule was seen on the inner side, evidently arising from the dura, besides other similar areas eroding the skull. The lymphatic glands in the mesentery, mediastinum and all through the body were enlarged. Bronchopneumonia of both lungs, caseous pleuritis of the right lung and warty endocarditis of the mitral valve were found. In the pelvis of each kidney was a hard yellow mass. The diagnosis at the time was tuberculosis, but Hand stated that he doubted the diagnosis himself.

Hand's second case, originally reported by Kay under the title "Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria," was in a boy, aged 7 years, who was healthy up to 4 years, at which time he had scarlet fever followed by a persistently discharging right ear. Four months after he had had scarlet fever, he had swollen cervical glands. When he was 4½ years old, the "gums began to separate from the teeth." This was followed by gradual loss of his teeth, beginning with the molars. At the same time soft spots appeared on the head where there seemed not to be any bone. When he was about 5 years old, exophthalmos was observed and shortly afterward polyuria and thirst suddenly developed. He passed 27 quarts of urine daily. He was much undersized for his age. It was observed that his breathing was stertorous. The bones were normal except for extensive cranial defects and similar changes in the maxillae. Kay evidently thought that the condition was due to a tumor at the base of the brain.

Hand's third case was in a boy, aged 4 years, who had had a tumor-like swelling removed from the left parietal region at the age of 2 years. There had been an absence of bone at this point, and the mass appeared to have arisen from the dura. The pathologic report of the tissue removed was "No gumma, no sarcoma, slight degree of inflammation, mainly a myxomatous change." Since then other swellings had appeared and exophthalmos, greater on the left side, had developed. In this report Hand stated that "no polyuria has developed as yet." The x-ray showed marked cranial defects, but "no involvement of the sella turcica," and "so no symptoms of diabetes insipidus."

Grosh and Stiffel's patient, a girl, aged 7 years, was weak and did not develop from the second year. She was markedly underweight and underheight. At 6 years she began having trouble with her teeth and with the left mastoid, which was opened and drained. Her mouth became sore with a bullous eruption on the gums, which necessitated the removal of some of the unerupted permanent teeth. Seven weeks after the operation on the mastoid she suddenly developed polyuria and thirst. Examination showed a bad condition of the teeth and gums, extensive cranial defects, dwarfism, typical diabetes insipidus and unilateral exophthalmos. There were similar bony defects of the maxillae and left ilium. When she was observed three years later, there was hardly any increase in her size, no obesity and the genitals were normal. The left ear was still discharging. The cranial defects had increased slightly. There was no x-ray evidence of involvement of the sella turcica.

Thompson, Keegan and Dunn's patient was a pale, poorly nourished boy of 9 years. At the age of 7½ years, he had a severe attack of measles. Following this, he was in a weakened condition and the gums became sore and the teeth

loosened Six months after the measles, excessive thirst and polyuria suddenly developed, persisted for only a few days and then disappeared At this time, soft spots on the right side of the head were observed A year after he had had measles, polyuria and thirst again appeared The boy was emaciated, with a sallow skin There was moderate exophthalmos, marked gingivitis and clean and sound but loose teeth The x-ray showed extensive bony defects of the skull, described as "geographical skull" The sella turcica appeared normal, but there were extensive similar defects in the maxillae, pelvic bones, upper portion of the right femur and ribs The body of the fourth lumbar vertebra was collapsed A tentative diagnosis of multiple myeloma was made This patient was under observation about eighteen months, during which time he grew progressively worse He became pale and emaciated, suffered from backache and pain in the left hip and walked with a marked limp, listing forward to the left Exophthalmos was marked The entire skull was soft and doughy, with only an irregular framework of supporting bony ridges The gingivitis was severe, and the teeth were held by soft investing tissue as the alveolar processes had been absorbed The x-ray of the chest revealed a diffuse increase in density, characteristic of chronic interstitial pulmonitis As death approached, the cough and dyspnea became more troublesome The end came suddenly, and was attributed to impaired circulation incident to intense pulmonary fibrosis At autopsy, the scalp showed fibrous adhesions The inner surface of the dura was mottled by dull yellowish white tissue, which took sharlach R fat stain The large yellow infundibulum stalk was fibrosed There was involvement of the petrous portion of the mastoid and the middle ear The ethmoid cells were obliterated by the same tissue growth The pathologic diagnosis in this case was "exophthalmos, decalcification of bones, fibrosis of the tuber cinereum, slight subacute inflammation of the pars posterior of the pituitary gland, chronic interstitial fibrosis of the lungs, hypertrophy of the heart, chronic passive congestion of the liver and spleen, hypertrophy of the kidneys and bladder" From their histologic study, Thompson, Keegan and Dunn considered the condition "inflammatory, rather than degenerative or a primary metabolic (endocrinologic) process"

Danzer's patient was a boy, aged 4½ years, who had recently had his tonsils removed He was miserable, having had repeated attacks of sore throat Two months after the operation, his mother first noticed soft tender spots on his head He was pale and stoop-shouldered, with exophthalmos, bad teeth, spongy gums and many soft spots on his head He complained of thirst and polyuria, which had evidently developed suddenly a year after the soft spots were first observed The x-ray showed extensive cranial defects and similar changes in the maxillae Danzer made no comment regarding the bones of the rest of the body and did not discuss the etiology

Kyrklund's patient, a girl, aged 12 years, was normal up to the age of 2 years, at which time she developed a cough, began breathing rapidly and became emaciated At 4 years she developed thirst and polyuria At the age of 7, she suddenly became fat, walked stiffly and complained of pain in the legs The skin of the head was so tender that she could not stand having her hair combed Growth was noticeably retarded, as was mental development She was dyspneic Her lips, hands and feet were cyanotic She had the typical appearance of dystrophia adiposogenitalis Examination showed that there were numerous cranial defects The long bones were normal The teeth were in bad condition and exophthalmos was present At autopsy, the scalp was adherent to the calvarium around the soft areas and when separated, yellow detritus-like material flowed out leaving cystlike depressions The inner table in these places was

eroded and the space filled with brownish yellow tissue arising from the dura. The dura had grown firmly to the inner table and showed yellowish brown, tumor-like thickenings. The region of the hypophysis did not show macroscopic changes, but there were growths in the brain stem behind the hypophysis of the same brownish yellow color. There were extensive changes in both lungs and pleura. "The structure of the lesions, on the whole, was similarly formed of connective tissue cells, part round cells, and some spindle cells. Lesions in the brain stem contained irregularly formed giant cells. The histological process did not simulate tuberculosis." Kyrklund considered the "condition due to a tumor of sarcomatous nature," and believed the "diabetes insipidus secondary to the growth in the region of the hypophysis."

CHRISTIAN'S SYNDROME AND XANTHOMATOSIS

I first associated this series of cases with xanthoma on purely clinical grounds. In 1922, Griffith reported "A Case of Xanthoma Tuberosum, with Early Jaundice and with Diabetes Insipidus." His patient showed defects of the membranous bones, exophthalmos and diabetes insipidus, as well as cutaneous lesions of xanthoma. Later this patient came to autopsy, and was studied carefully by Wiedman and Freeman.

Xanthoma, supposedly a rare disease, has been the subject of a surprising amount of study. While this adds a great deal to the better understanding of the varied problems of xanthoma, the many researches lack the clinical evidence, which this unique group of cases, "Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus," might contribute.

HISTORICAL CONSIDERATION OF XANTHOMA IN RELATION TO CHRISTIAN'S SYNDROME

As there is little discussion of xanthoma in works on general medicine and so much of interest in the dermatologic and special pathologic literature, a consideration of the investigations which have led up to the present interpretation of this process is important. A study of the anatomic and microscopic features will establish the identity of this unique syndrome, as well as contribute to a better understanding of the pathogenesis.

GENERAL ACCOUNT OF THE CLINICAL PICTURE

Constitution—Several clinical forms of this condition, characterized by yellow to yellowish brown lesions containing special large cells, have been observed and described in the dermatologic literature, the one most frequently noted being the familiar orange yellow plaques or nodules on the eyelids—xanthoma or xanthelasma palpebrarum. This variety occurs most often in adults past middle age. Less often, and especially in young children, a generalized eruptive form, xanthoma multiplex, is seen. Associated with the cutaneous manifestations are

tendinous, peritendinous and periarticular lesions xantho-myeloma of the tendon sheaths At times a special generalized eruptive form appears in glycosuric subjects xanthoma diabeticorum In a few instances, as a result of studies made at autopsy, nodules and plaques involving certain internal structures are observed generalized visceral xanthoma or xanthomatosis The lesions in this type may appear on the various mucous membranes, there may be involvement of the cardiovascular system, especially the inner walls of the larger vessels and heart valves, or of the serous surfaces, the periosteum, pleura, pericardium, capsule of Glisson, dura and peritoneum Finally, there are instances in which, as a result of histologic study, the mesenchymal portion (reticulum and endothelium) of certain organs—the liver, lymph nodes, spleen, bone marrow, suprarenals, hypophysis, thymus, pancreas and lungs—are found to be affected by the process This form occurs at all ages and is frequently associated with icterus, glycosuria or diseases of the kidney in adults In young children in whom icterus and glycosuria are rare complications, these cases are often congenital or there is a family history This type is observed sometimes with, often without, skin manifestations

General Comment—Xanthoma was first described by Rayer, in 1836, under the French title—"Plaques jaunâtres des paupières" Sixteen years later, Addison and Gull published their monograph "Vitiligoidea" In 1863, Erasmus Wilson proposed the name xanthelasma, meaning yellow plaques, and W F Smith, in 1869, because of the tumor-like appearance of the yellow nodules, gave the name now generally used, xanthoma

The early study was, for the most part, clinical, and was concerned with the separation of the different forms, the consideration of symptomatology and the report of interesting cases Addison and Gull first described the multiplex variety, studied the relationship to diseases of the liver, and observed a case associated with glycosuria Balzer described the tumor-like forms arising from tendinous, peritendinous and periarticular surfaces The works of Pye-Smith, Murchison, Fagge, Crocker, Chambard and others made known the mucous membrane and visceral localizations as they occur in adults To these varieties Hutchinson, Sangster and Crocker, a committee appointed by the London Pathological Society in 1882, added juvenile xanthoma, separated because of its occurrence before puberty

Crocker published a good clinical report of the early dermatologic literature, and recently G Levy reviewed the entire subject Weber and Stewart presented suggestive clinical discussions, Wustmann, a consideration of the histopathogenesis of the nodular lesions, Aschoff, Kammer, Kawamura, Chalatow and Versè have made important contributions In our own literature, Beeson and Albrecht have reviewed the multiplex

variety, and Knowles and Fisher, this form as it occurs in early childhood. McWhorter and Weeks have considered the tumor-like forms arising from tendon sheaths from the surgical point of view. Major has reviewed the cases associated with glycosuria, and recently Oppenheimer and Fishberg have discussed a case of this type in its relation to the reticulo-endothelial system. Their patient was a girl, aged 6 years, who had extensive visceral involvement.

Symptomologic Considerations—Many cases of unusual clinical interest with lesions not confined to the skin were recorded in the early literature. Von Graefe and Virchow observed yellow plaques on the mucous membranes of the cornea and conjunctiva. A patient of Pusey and Johnstone had corneal involvement. Crocker observed yellowish-white patches on the tongue of an infant, aged 3 months. Dyer and also Fordyce saw patients with involvement of the lips and buccal mucous membranes. Posner's patient had lesions of the gums and palatine arch. In Hardaway's patient, besides involvement of the penis, scrotum and the area underneath the nails, the xanthomatous eruption was distributed like herpes zoster over the ninth and tenth ribs. Kreibeck recently described a similar zosteriform xanthoma associated with lesions of the mucous membranes and skin. Pusey and Johnstone's patient also had nodules in the larynx. Murchison recorded a case in which lesions of the skin were associated with nodules the size of peas about the hilum of the liver and splenic capsule, both these organs being enlarged as well as the lymph nodes and the spleen. There were also yellow patches on the heart valves and yellow areas in the posterior wall of the stomach. In addition to an extensive eruption of the skin, Pye-Smith observed xanthoma-like areas on the mucous membranes, peritoneum and about the hilum of the liver and splenic capsule, "associated with jaundice." As early as 1872, however, he noted that it was not real jaundice and remarked that "the lesions about the gall-bladder looked like atheroma of the arteries."

Clinical and Symptomologic Considerations Concerning Syndrome—There are a number of cases recorded in the literature that are of interest in connection with the syndrome I have described. Notable among these is a somewhat similar group occurring in adults, with extensive involvement of the serous surfaces, reported by Pfoescher and Meredith, Dietrich, and Nothen.

Dietrich's patient had exophthalmos and was thought to have had some pulmonary disease. He died of cardiac failure. The autopsy revealed what Dietrich called fibroxanthosarcoma. There were retro-peritoneal masses extending along the spine from the abdominal to the thoracic cavity. Yellow nodules, the size of kernels of corn, were thickly scattered over the surface of the liver, splenic capsule, the pleura and pericardium. Larger yellow masses were found in both orbits and

surrounding the vessels at the base of the brain. The hypophysis was pushed out of the sella turcica by the "tumor masses."

Yellow, tumor-like, xanthoma nodules involving the dura and sometimes associated with exophthalmos have also been mentioned by Pinkus and Pick, Krich and Weber and Schmidt.

There is no mention of diabetes insipidus in Pfoescher and Meredith's, Dietrich's, or Nothen's cases, but such cases have been recorded by Crocke, Fitch, Spillmann and Watrin, Pusey and Johnstone, Turner, Davidson and White and Griffiths. Probably the patients of Weber and Schmidt, Siemens and Fahr and Stamm had this complication.

Crocke's patient had diabetes insipidus and "gouty tendencies." Fitch's patient was an adult and had xanthomatous changes involving the hilum of the liver, with jaundice as well as diabetes insipidus. Besides extensive lesions of the skin the case of Turner, Davidson and White showed involvement of the tongue, epiglottis, trachea, bronchi, lungs, mucous membranes of the stomach, mediastinum and pituitary region. This patient also had diabetes insipidus with yellow xanthoma nodules surrounding the hypophysis. Pusey and Johnstone's patient, a boy, aged 17, besides extensive xanthoma lesions, showed a marked degree of dwarfism as well as diabetes insipidus. Spillmann and Watrin's patient, a girl, aged 9 years, with generalized papular xanthoma, was undersize for her age. She had thirst and polyuria.

Both Pusey and Johnstone's and Spillmann and Watrin's cases showed features similar to those of "Christian's syndrome," but Griffith's case, already referred to as representing "defects in membranous bones, exophthalmos and diabetes insipidus," was the most striking.

Griffith's patient, a much undersized boy of 9 years, had been healthy and normal up to 2 years. At the age of $2\frac{1}{2}$ years, he had pertussis. At 3 years he had a temporary enlargement of the abdomen and "yellowness." Growth was evidently retarded from this time. At 8 years he had another attack of jaundice and swellings on the head following contusion, and an eruption appeared all over the body. The child was undernourished and underdeveloped, with extensive cutaneous xanthoma eruption, evident exophthalmos, marked irregularities of the teeth, defects in the skull and typical diabetes insipidus. Autopsy revealed yellow masses about the hilum of the liver and arising from the dura. The hypophysis was displaced by the xanthoma mass.

Berkheiser reported a case under the title "Multiple Myeloma of Children," which obviously also belongs in the group I am describing.

Berkheiser's patient was a girl, aged $3\frac{1}{2}$ years. She had had a normal first year, except for a mild attack of measles at 9 months. Exophthalmos was first observed when she was 16 months old. She complained of pain in the right leg, hip and arm, and difficulty in walk-

ing She was irritable and gave a history of bed wetting The x-ray revealed extensive bony defects of the cranium, the pelvis, the upper portion of the right femur and the lower portion of the left humerus Interest in this patient was directed to the orthopedic condition There was no mention of the urinary symptoms, but a study was made of one of the lesions which will be considered later

Other cases are recorded in the literature, most often occurring in young children but sometimes in adults, that could be brought into relationship with this unique syndrome purely on clinical grounds The juvenile type I have described unites the entire group in a striking manner This is shown more fully in the histologic study

PATHOLOGIC CONSIDERATIONS

Microscopic Changes—In the early literature, the histologic studies of the lesions were associated with the clinical observations Most interest centered about the character of special cells Waldeyer, Virchow, Kaposi, deVincentis, Chambard and Touton described the morphology of these cells According to Chambard, the xanthelasmic cells are variable in size and form, with an abundance of protoplasm and small darkly staining nuclei In the fresh state, the protoplasm is loaded with small fatty droplets Treated with ordinary fixing reagents, which dissolve out the fat, the protoplasm becomes a fine areolar network giving a foamy or vacuolated appearance, hence, the name "foam cell" or "Schaumzelle"

These cells never show karyokinesis They are found free in the layers of connective tissue, frequently surrounding the blood vessels, or are grouped in islets separated by fibers of connective tissue Sometimes they are fused to form a multinuclear mass with nuclei disposed as a corona or demicorona giving the aspect of giant cells Associated with these cells, there is a variable connective tissue reaction and sometimes round-cell infiltration Occasionally typical foreign body giant cells with nonfoamy protoplasm and more scattered nuclei occur in relation to fatty crystals

This structure appears as a diffuse process, or is grouped to form the xanthoma plaques and nodules Early in its development the xanthoma cells, with increased vascularity, are in excess, while in the older nodular lesions the connective tissue growth predominates, appearing greatest in the larger and firmer lesions

The fatty substance exists, generally, either as fine granules or as round droplets, but sometimes as crystals in small rods or fine needles, united in clusters It is for the most part contained in the cells, although occasionally it is found in the intercellular spaces

These fatty granules usually present themselves under two aspects (a) those which stain poorly with osmic acid, taking a brown color, stain

orange with sudan III, and show double refraction with polarized light, i e, cholesterol fatty acid esters, (b) those which stain deep black with osmic acid, turn red with sudan III, and remain dark when the prisms of the polariscope are crossed, i e, neutral fats or glycerine fatty acid esters (Darier)

These two granular forms are found to exist together, but are irregularly and diversely distributed, and at times there are remains of red blood cells and iron pigments in these lipid-containing cells (indicating phagocytic properties) They owe their appearance to the substances which infiltrate them and, in swelling, separate the cytoplasm The perivascular distribution, variable connective tissue reaction, sometimes round-cell infiltration and the presence of fatty and pigment granules and giant cells produce the varied appearance of the lesions It is these special lipid-containing cells which particularly characterize the varied xanthoma manifestations

Microscopic and Clinical Changes—Chambard, Touton and Torok observed xanthoma cells in the diverse skin lesions Dor observed the same cells in the nodular forms arising from tendinous, peritendinous and periauticular surfaces Chvostek first found foam cells in yellow nodules about the hilum of the liver Coats early observed foam cells in the spleen of diabetic persons with lipemia Particular attention was not given to these cells in the inner organs, until Schultze reported in 1912 "Concerning Large Cell Hyperplasia in a Case of Diabetes with Lipemia" Since then an entire new series of cases has been brought into relationship with the clinical forms already described Some of these cases show and some do not show skin manifestations Aschoff, Kawamura, Marchand and Chalatow made important observations in this regard

In Schultze's case, the entire splenic pulp was replaced by foam cells, and other organs were not involved Lutz reported two similar cases, one showing atheroma in the aorta and the other, changes in the lungs Schultze and Lutz considered this condition related to Gaucher's disease

Marchand found lipid-containing cells in the spleen and lymph nodes and was the first to observe this change in the bone marrow Williams and Diesbach found lipid-containing cells in the spleen, liver, lymph nodes and suprarenals In M Smith's patient they were mostly confined to the spleen, but to a small extent appeared in the liver and lymph nodes Oppenheimer and Fishberg's patient, previously mentioned, showed much more extensive changes There were lipid-containing cells in the spleen, liver, endothelium of the aorta, adventitia of the cutaneous vessels, and also changes in the kidneys and mitral valve These changes all occurred in patients with diabetes mellitus associated with lipemia

There is still another group of cases that may be brought into relation with xanthoma. In 1914, Niemann described a condition in an infant which he regarded as histologically different from Gaucher's disease, but which was similar to the large cell hyperplasia reported by Schultze. Siegmund described a similar change in an infant, aged 9 months. He observed lipid-containing cells at the hilum of the liver and spleen. The Kupffer cells of the liver, the reticulo-endothelial cells of the spleen, the bone marrow, heart valves, glomeruli of the kidney, and excretory tubules also were involved. Knox, Wahl and Schmeisser and Bloom have reported similar cases.

The lipid-containing cells in this group of infants are the most extensive in distribution. According to Bloom, they are observed in the spleen, thymus, mucosa of the intestines, free in the alveoli of the lungs and in the walls of the blood vessels of the lungs, kidneys, pancreas and in the Kupffer cells of the liver. M. Smith added that they were also found in the bone marrow and brain tissue in one case. In this group there is considerable phosphatid lipid but also some double refractive lipid. In the literature this series has usually been referred to under the title of Niemann's disease, and has been regarded as different from Gaucher's disease (Mandelbaum, Bloom and Oberling).

A case reported by Fahr and Stamm has generally been included with the series just described, but I wish to show that it also closely resembles, clinically and histologically, the group I am discussing, Christian's syndrome.

Fahr and Stamm's patient was a weak, undernourished, underdeveloped girl, weighing 18 pounds (8,164.6 Gm.) at 3 years. Fahr thought that she had some disturbance of carbohydrate and protein metabolism. He also questioned whether there might not be a hypophyseal disturbance. She had always had thirst and had not grown. Her skin was dry, and the hair, which had turned a lighter color, was falling. She died in uremic convulsions. At autopsy the lipid-containing cells were most noticeable in the lymph nodes of the "lymphatic portal ring," less in the spleen, and least in the Kupffer cells of the liver.

In my first case there were lipid-containing cells in the lymph nodes, Kupffer cells of the liver, supraenals, few in the kidneys and thymus and many in the lungs and the nodular lesions of the dura, peritoneum and pleura. In Griffith's patient, examined by Weidman and Freeman, there were extensive xanthomatous changes of the skin, lymph nodes, liver, bile ducts, lungs, pineal gland, infundibulum, pituitary and dura. Possibly the glia cells were involved.

Microscopic Changes Concerning the Syndrome—Weidman and Freeman stated "that the organs in their patient reflected only the general sclerosing effect which makes many of the tissues resemble, under

the microscope, those of a subject dying of senility" This is why most of the cases in the series here presented, which have come to autopsy, have not been identified with xanthoma In their histologic studies of xanthoma skin nodules, Pollitzer and Wile demonstrated that the early lesions are made up almost entirely of foam cells, lesions a little more advanced show foam cells and spindle cells with considerable connective tissue reaction, and finally, some of the older lesions are composed almost entirely of spindle cells and fibrous tissue

In the case that Thompson, Keegan and Dunn described, there was such an advanced process that in many places only spindle cells, secondary reactions and fibrosing effects were observed Their patient showed extensive xanthomatous changes about the hypophysis, base of the brain, dura and lungs, similar to the changes in my first case, only in a later stage of development The condition of the little girl described by Berkheiser represents a less advanced stage and, as he says, was regarded by Maximow as xanthomatous in character In Kyrklund's case, the underlying process was not recognized for the same reason, but I believe that it represents the same pathologic change with the variations which are characteristic of this condition

In this group, another case reported by Schultz, Weimbert and Puhl under the title "A Granuloma-like System Disease of the Hematopoietic Apparatus Hyperplasia of the Reticulo-Endothelial System" should be included Their patient, a girl, aged 2½ years, had extensive defects of the bones and dwarfism The histologic study showed that the process was quite advanced The nodular lesions arising from the dura had all changed to fibrous tissue The lesions in the orbit and at the base of the brain looked like thickened tendon The yellow nodules and diffuse changes in the lungs resembled those found in the lungs in my first case There was more extensive involvement of the organs, especially the bone marrow and spleen, and more tendency to a nodular type of lesion in the organs, than in any of the cases I have previously described Schultz, Weimbert and Puhl considered the condition a disease of the reticulo-endothelial system and supposed an infection of unknown type to be responsible

Study of Microscopic Changes, Conclusions—The study of the microscopic changes, besides bringing into relation with xanthoma several forms not previously recognized as such, determines certain other facts regarding the chemistry and character of the lesions

1 Xanthoma represents a mixed steatosis in which, although double refractive cholesterol esters are most often observed, phosphatid lipoids and other more complex lipoids (lipoproteins in Gaucher's disease) are also concerned, and these lipoids are always in association with glycerin fatty acid esters

2 The lesions are extremely variable in their histologic appearance. At first they are made up largely of foam cells and later, almost entirely of spindle cells and connective tissue. In the early stage the lesions may be vascular, while in a later stage the vascular supply is limited. In the older lesions there are frequently no lipoid-containing cells, only special forms of fibrous tissue, and cellular reactions and secondary changes occur which mask the picture generally.

3 The process is an extensive one, not simply confined to the skin and certain internal structures, such as the mucous membranes, the walls of the large vessels, heart valves and serous surfaces, but it may also involve the mesenchymal portion of the blood and lymph vessels generally.

Finally, the study shows that this condition occurs at all ages, usually appearing as discrete nodular lesions in the slowly evolving adult forms and as a more diffuse process in the rapidly developing infantile cases.

The significance of these observations will be more fully discussed in the consideration of the pathogenesis.

PATHOGENESIS IN RELATION TO HYPERLIPOIDEMIA AND THE RETICULO-ENDOTHELIAL SYSTEM

Pathogenic Theories—Many opinions have arisen as to the nature of the varied xanthoma manifestations. Addison and Gull regarded xanthoma as a local disease. Hutchinson, observing the frequency of jaundice, thought that diseases of the liver and gall passages were of etiologic importance. Hilton Fagge and Pye-Smith, finding visceral lesions, regarded xanthoma as a systemic process and referred icterus and glycosuria back to the visceral localizations.

Most of the early studies disregarded these clinical symptoms in favor of various cellular theories. Potain considered the cutaneous lesions enlarged skin glands. Unna and Balzer, observing giant cells, were inclined to believe in an infectious origin. Chambard and Renaud proposed that the xanthoma cells might be connective tissue cells, analogous to macrophages loaded with fat. Chambard and Torok, observing round cells, especially in the diabetic form, considered the lesions of inflammatory nature. The most frequent interpretation, however, was neoplastic. For Virchow, xanthoma was a neoplasm of the connective tissue with fatty deposits or fatty degeneration of cells, and Touton. Koebner and de Vincentis held similar opinions but regarded the cells as of endothelial origin. Torok considered xanthoma as a neoplasm of the connective tissue resulting from the proliferation of cells arrested in an embryonic state. Crocker also regarded xanthoma as a neoplasm of the connective tissue. He considered the inflammation primary and the connective tissue growth secondary and the whole process of toxic origin.

Potain and Quinquard early proposed a humeral theory in relation to the hepatic dysfunction. Panzer, in Stoeck's laboratory, first identified double refractive lipoids in the fat filled cells. Pinkus and Pick, finding double refractive lipoids in the various xanthoma lesions, declared hypercholesterinemia the probable cause of xanthoma. In a second research, in which they examined all the different xanthoma pictures, they concluded that an infiltration of connective tissue elements, reticulum and endothelium takes place. They believe that the nodules were neoplasms of the connective tissue, but wished to designate the change by the term "xanthomatosum," as a condition that might affect any new growth. In discussing his extensive case, previously mentioned, Dietrich objected to Pinkus and Pick's use of an adjective to designate this condition. He thought that there was a small group of xanthofibromas.

Hypercholesterolemia—The actual demonstration of hypercholesterolemia was due to Chauffard and Laroche. They found hypercholesterolemia in several patients with xanthoma, as well as in an icteric patient afflicted with xanthoma. Chauffard and Laroche stated "Special as this process is (the formation of cholesterol deposits), it is not, however, without an analogy in pathology and nothing could be more truthfully compared to it than the change which we find in another great humeral illness, gout. There also, a specific cutaneous deposition, the tophus, discloses an excess of uric acid circulating and then fixed. Each of these two toxemias makes itself concrete, as it were, in its own place of election, but the process is identical and the end is an aseptic and specific infiltration, so that one can conclude that xanthoma is to hypercholesterinemia as tophus is to an excess of uric acid contained in the blood serum of the gouty patient."

Hyperlipoidemia, Clinical Consideration—Hyperlipoidemia, especially hypercholesterinemia, is now generally regarded as the most common fundamental cause of xanthoma. Since the original observations of Chauffard and Laroche in 1910, this has been repeatedly verified—by Schmidt, Aining and Lippmann, Burns, Levy, for the multiplex varieties, Major, Mook and Weiss, for xanthoma diabeticorum, Weil and Kirch, for the tumor-like forms arising from tendon sheaths, Spillmann and Watrin, and Griffiths, for the juvenile type I have described. Harrison and Whitfield reviewed this subject in 1923.

The cholesterol value in Griffith's patient was 397 mg per hundred cubic centimeters of blood serum, in the similar case of Spillmann and Watrin, there were 595 mg per hundred cubic centimeters of blood serum. In my first case, examinations were not made for cholesterol, but dural plaques examined in this regard showed high cholesterol content. In my second case, repeated determinations of cholesterol

were made. They varied from 315 mg per hundred cubic centimeters of blood serum, in October, 1926, 256 mg (250 mg, digitonin method), in April, 1927, to 111 mg (Myers and Wardell method) in October, 1927.

The analysis of the clinical observations in relation to hypercholesterolemia is of interest. In the investigations of Schmidt and Levy, in which entire families were examined, it was found that hypercholesterolemia manifests itself in a different manner, according to the individual, it produced biliary lithiasis in one, atheroma in another, and brought on ocular symptoms in a third. It is only in certain subjects that it produces either xanthoma palpebrarum, or the cutaneous cholesterol infiltrations which result in the multiplex variety, or in extremely rare cases, in the tendinous, peritendinous and periarticular and visceral forms (Levy).

These investigations also determined that cholesterolemia, though considerable, does not always result in xanthoma eruption. This suggests the possibility of certain accessory factors, such as trauma and friction, or infection. Clinical observation permits the recognition of such accessory factors. Various authors have verified the fact that the skin eruption localizes, by preference, in places exposed to repeated trauma or friction, such as the elbows, knees, buttocks, shoulders and palms. Darier believed that he was able to attribute palpebral localization to frequent folding and rubbing of the eyelids. Chauffard and Laroche observed the eruptions appearing at the point of injections of sodium cacodylate in a patient with icterus. Major found it following mosquito bites. In a case described by Nicol, cutaneous xanthoma occurred after a quinine exanthem. In the cases of Hardaway and Kreibeck, the lesions were distributed like those in herpes zoster. Such an eruption probably accounted for the localization. The raised and thickened vaccination scars often observed sometimes result from the same cause.

In several of the group described trauma may have antedated the lesions on the head, but the process is too extensive for all of the lesions to be accounted for in this manner. In generalized visceral xanthoma in an adult diabetic patient, Lubarsch considered that for the lesions to develop, it was necessary for cholesterol to show stasis and accumulate for a long time, mainly in the lungs. This might have happened in the cases here described. As shown by the studies made at autopsy, there has invariably been a marked degree of pulmonary fibrosis and xanthomatous change in the lungs. In case 1, the fibrosis was so advanced that it gave the impression of being the primary lesion.

In this connection the secondary importance of infection is apparent. Weber wrote that "it is highly probable that a person may have a

hypercholesterolemia for years without developing xanthoma lesions, but some influenza-like infection may give rise to inflammatory changes and be followed by lipid deposits." There was no evidence of syphilis or tuberculosis in the group of cases I have described, but several authors have suggested the possibility of these infections playing such a part. Various acute infections antedated the onset in most instances and the frequency of bronchial infections at this age suggests their importance as predisposing factors. In case 2 it is apparent that the condition was aggravated by acute infections. Fahr believed that infectious irritation was important in the majority of cases. Schultz, Wernbter and Puhl considered an infection of unknown type responsible in their case. Aschoff said that the question is still open, but he added that he could agree if Fahr should consider other unrecognized irritative factors. I shall discuss the relation of infection further in the section on animal experimentation.

About half of the generalized visceral forms of xanthoma have been considered as related in some way to icterus and disorders of the liver in general, diabetes mellitus or certain diseases of the kidney. It is important to note that in none of this group of cases have these conditions been present. In Griffith's patient there was jaundice, but it was without doubt secondary to the xanthomatous changes about the hilum of the liver as Griffith himself believed. In Fahr and Stamm's patient, death resulted from kidney complications, and lipid changes were found in the kidneys.

Chambard early proposed a special diathesis for xanthoma, Arning and Lippmann regarded as "essential or idiopathic" those cases not associated with icterus, glycosuria or pregnancy. This applies especially to the juvenile form in which familial tendencies are frequently observed. So far as the group reported has been studied, there have not been clinical records of familial tendencies. The examinations of the blood in the members of the family in case 2, however, were suggestive. The mother had a blood serum cholesterol of 272 mg per hundred cubic centimeters, one brother had a chronic valvular cardiac disease, and a single determination of cholesterol showed 175 mg per hundred cubic centimeters of blood serum.

The clinical form which xanthoma assumes is considered as related to the intensity and persistence of the process, and I wish to add that it is also related to the age of occurrence. Usually the most extensive manifestations are found in subjects with a particularly elevated cholesterol. Especially in xanthoma diabetorum, in which the cholesterol value generally is high, the eruption is apt to be extensive and frequently develops rapidly. On the contrary, under the influence of diet and, more strikingly, under the influence of treatment with insulin, the lesions often disappear, coincident with a decrease in blood lipids.

In case 2, in which at the time of my first examination there was a moderate increase of blood cholesterol, x-ray examination showed moderate increase also in the destruction of bone. During the past year, while the blood cholesterol has been low, there has been a most remarkable lessening of the bone destructive process as shown by the roentgenograms. The defect in the bone at the vertex of the calvarium has filled in to such an extent that it can only be located with difficulty and the large areas at the base of the skull have been almost entirely regenerated. Coincident with this, the patient, instead of being irritable, is happy and active and is without pain or discomfort. He has increased in height $3\frac{1}{2}$ inches, in contrast to his growth of less than 1 inch during the preceding twelve months, and the polyuria and polydipsia have decreased (compare *C* and *E* in figure 10).

Oppenheimer and Fishberg, observing the disappearance of extensive xanthoma in a young diabetic patient as the blood lipid diminished under the treatment with insulin, stated that it proved for them the dependence of xanthoma on an excess of lipoids in the body fluids.

This is the generally accepted view, but cases have been reported by Arzt, Rosenthal and Braunish, Siemens and Dubs in which the two conditions were not present at the same time. These investigators considered the relationships between cholesterol in the blood and in the tissues as not essential. They explained the xanthoma manifestations either on the ground of local factors, mechanical and other irritations of the tissues, blood and lymph stasis and local inflammatory changes, or the influence of the chromaffin vegetative nervous system, such as an acquired biologic characteristic of cells, with respect to metabolism of cholesterol.

In regard to these negative observations, Levy expressed the opinion "that it is preferable to make note of these facts without trying to interpret them. Perhaps they will find an explanation in the doctrine of hypercholesterolemia, or on the contrary, they may put us on the track of factors which are still unknown."

The mechanism with which the body controls metabolism of cholesterol is complicated. Cholesterol in the blood undergoes great variations. In all metabolic disease individual symptoms undergo varied accentuations, so that there is no necessary parallelism between the picture of xanthoma and the increase in cholesterol. Cholesterol is only the starting factor. During the period in which the xanthoma remains stationary, the cholesterol is at a low level. In such instances, the association of xanthoma manifestations with increase in cholesterol is seen in the chemical structure of the lesions.

Hypercholesterinemia and Animal Experimentation—A long series of animal experiments (by Anitschkow, Aschoff, Kawamura, Bailey,

McMeans, Chalataw, Zinzerling, Verse and others) furnish a most important confirmation of the clinical observations here discussed. They also demonstrate that pathologic degrees of hypercholesterolemia can be produced in animals by feeding diets rich in cholesterol, which suggests that there are new dietetic problems to consider in the feeding of infants and children.

Anitschkow, feeding rabbits on a diet rich in cholesterol, caused lipid storage in the interstitial cells of the spleen, bone marrow, lymph nodes, Kupffer cells of the liver, walls of the large vessels and in extreme cases, in the connective tissue cells of the skin. He produced what in many respects could be regarded as an imitation of xanthoma in each of its many forms. These experiments confirm the clinical observation that lipid storage varies with the duration and intensity of the process and that it occurs, preferably, in regions especially exposed to trauma and strain. They also demonstrate that under normal conditions lipid is not stored in the presence of an aseptic irritative process but that it occurs when there is hypercholesterolemia. On the other hand, they demonstrate that lipid storage appears in the presence of suppurative processes under otherwise normal conditions. In such instances, it results from the absorption of cholesterol locally liberated by the destructive effects of the suppurative process.

In another series of experiments, Anitschkow demonstrated that hypercholesterinemia, however transient, provokes lipid storage. This confirms the fact that even though the subject may not at the time have hypercholesterolemia, xanthoma manifestations always indicate that it had been present at some former period.

Still another problem of clinical importance is explained by these experiments. Xanthoma is characterized by two processes, lipid infiltration with the formation of xanthoma cells and connective tissue proliferation. For a long time, the succession of these processes has been in doubt. Some have regarded the lipid infiltration as primary, while others affirmed that it is secondary to inflammation of the intima. According to Anitschkow, both views are right. On the one hand, the cholesterol grafts itself on previously injured surfaces, while on the other the lipoids acting on an artery which has been normal up to this time cause an irritative state and provoke a hyperplastic reaction. Zinzerling agreed that it does not require either injury or inflammation to bring about these changes, but that the irritating effect of cholesterol alone may produce the hyperplastic reaction.

These experiments demonstrated that lipid storage (xanthoma manifestations) may appear in any part of the body in which there is activity of the cells. It extends to the interstitial tissue of the inner organs, suggesting an analogy to changes found in man. There may be a difference between what takes place in animal experimentation and

what actually occurs in pathologic changes in man, nevertheless, animal experimentation throws light on the nature of the condition as it is found in man

The Reticulo-Endothelial System and Xanthomatosis — Since Aschoff and Landow in 1913 proposed grouping certain body cells according to their functional properties rather than their morphologic characteristics, they have been called the reticulo-endothelial system. This cellular system, characterized by its exaggerated ability to ingest, is sometimes spoken of as a storage system or, since substances come from the blood stream and purification takes place, as a blood purifying system. Metchnikoff early studied the behavior of these cells. He differentiated between the circulating ameboid cells of the blood, the polymorphonuclear leukocytes, or microphages, and the relatively fixed ameboid cell of the tissues, or macrophages, and emphasized the highly phagocytic properties of the latter group. Possibly he had some notion of a special system, at any rate, he clearly appreciated the importance of these cells, not only in phagocytosis of foreign materials but in their part in processes of inflammation and immunity.

According to Aschoff, the reticulo-endothelial system is the intermediate agent of metabolism between the blood and the tissues. Besides playing a prominent part in metabolism, and especially in lipid metabolism, it is probable that this system of cells is concerned in formation and destruction of blood, and that iron injected into the blood stream is stored in the reticulo-endothelial cells. It is also probable that the formation of bilirubin occurs within these cells. (See recent reviews by Aschoff, Sachs and Jaffó) While, as Oberling observes, this system is not a physiologic entity, as all of its elements do not behave in a similar manner and some authors hesitate to call it a system, nevertheless, a consideration of xanthoma manifestations and lipid metabolism, in the light of this hypothesis, contributes much to the understanding of the pathogenesis and the microscopic changes as well as the clinical manifestations of xanthoma.

The experiment which particularly led to calling the special phagocytic cells a system was the work of Ribbert, who in 1904 demonstrated by injecting lithium carmine intravenously, intraperitoneally and subcutaneously that the coloring matter, although partly eliminated by the kidneys, was partly stored in certain cells of the organism and always in the same cells for a given organism. Ribbert also observed that the cells which were vitally stained were able to take up other substances injected into the blood stream, e g, iron and lipoids. Aschoff made the first report of the investigations of his pupil, Kiyono, on the vital staining of these cells in normal and pathologic tissues. He introduced the term histiocyte to designate mesenchymal mononuclear phagocytic cells and described their behavior in detail.

Included in the reticulo-endothelial system are three main classes of cells, which are closely related genetically (1) the reticulum cells of the splenic pulp, lymphatic tissue and bone marrow, (2) the endothelial cells of the liver capillaries, lymph sinuses, splenic sinuses, bone marrow, suprarenal capillaries and hypophyseal capillaries, (3) the phagocytic cells in the connective tissue, which include Ranvier's clasmotocytes of areolar tissue and Marchand's adventitial cells surrounding the blood vessels. Cells of this character may enter the blood stream, where they are present as monocytic elements (i.e., endothelial leukocytes of Mallory)

The essential microscopic characteristic of the varied xanthoma manifestations are the large bright foamy (xanthoma) cells. A question that has attracted much attention concerns the origin and nature of these cells. At one time, owing to a superficial resemblance, it was supposed that in some way they might be related to sebaceous gland cells. They have been regarded as a special kind of tumor cell and even a parasitic origin has been suggested. Most often, however, they have been considered as cells of endothelial origin showing a peculiar kind of fatty change. Pinkus and Pick, Aschoff, Pollitzer and Wile, Kawamura and Fahr observed that these foamy cells are of reticular and endothelial origin and possess phagocytic properties. Anitschkow, in his feeding of cholesterol to rabbits, definitely demonstrated their identity with the histiocytes by staining them vitally with pyril blue and trypan red at the same time that he transformed them experimentally into xanthoma cells. He further demonstrated that the cells containing anisotropic bodies all belong to the reticulo-endothelial system. A review of the study of the microscopic changes shows that lipid-containing cells (xanthoma cells) have been observed in all parts of the reticulo-endothelial system, and that they are extensively distributed in the group of cases I have described.

It is of interest to note that the same cells are the essential cells in the lesions of tuberculosis and in the lepra nodule and the specific lesion of Hodgkin's disease, the hyperplastic reaction resulting from different causes.

Whether the presence of lipid in the cells is a sign of degeneration or of infiltration or whether lipid is manufactured in the cell itself is still a much debated question. Virchow thought these fatty changes were a mark of degeneration. Kaiserling and Orgler, who first described double refractive bodies, observing them in the cells, believed that they originated there. Pick and Pinkus, Aschoff, Kawamura and Anitschkow, noting that the xanthoma cells have phagocytic properties, regarded the change as an infiltrative one. "It is not a passive one, however, as it is due to lipoidophagic activity on the part of the cells themselves" (*Weber*)

Even today there are different views regarding the presence of lipoids in the cells. Aschoff thought that the reticulo-endothelial cells had an especial affinity for lipoids. Heck recently expressed the opinion that the appearance of cholesterol in the tissues and its appearance in the blood have a common origin, but that at times they may occur independently of each other. For him, the fundamental principle of retention of cholesterol is a physiologic change in state, which differs in every case. As to a special cell affinity, as proposed by Aschoff, Fah1 said that this is only a theory. Most of the recent observers regard the change as exclusively an infiltrative process, the truth of which is supported by animal experimentation. Oberling expressed the opinion that it is purely chemical, a view made acceptable by the present understanding of the reticulo-endothelial system.

Levy drew a striking analogy between the experiments of Ribbert and Anitschkow. "In both cases a colloidal substance injected into the veins of a rabbit is stored by a biologic system characterized by its elective phagocytic properties. In the two cases, moreover, the accumulation of phagocytosed substances, whether carmine or cholesterol, occurs with predilection in inflamed tissues or in tissues in an irritated state with tendency to proliferation. In a similar manner, the substances introduced into the skin of rabbits by Ribbert, Lebedew and Basten resulted in the formation of cholesterinophagic or carminophagic nodules which did not differ from one another, except in the nature of the substance injected." In conclusion, Levy observed "It is not too much to say that the xanthoma manifestations result from the 'vital staining' of certain parts of the reticulo-endothelial system by cholesterol esters and from the reaction this lipid infiltration provokes."

GENERAL COMMENT IN RELATION TO THE SYNDROME

In view of the length of this study, I have not considered certain problems that are still unsolved. It is evident that there are no definite conclusions as to why lipoids accumulate in the body fluids. Abnormal congenital predisposition, as usually ascribed to the infantile group of this condition, is purely a supposition. There may be some hormone influence or disturbances of excretion, though these suggestions have not been proved. Physiochemical conditions are also considered as possible factors. Without doubt, alimentation plays a part, as hypercholesterinemia can be produced by types of nourishment. Lipoid metabolism has not been fully worked out, nor has its association with general metabolism been completely explained. Nevertheless, this consideration of Christian's syndrome, in connection with facts already in the literature, makes it possible for certain conclusions to be drawn

regarding the circulation of lipoids in the body fluids and the significance of this striking symptom complex

The immense amount of microscopic and biochemical research on the subjects involved as well as the many points of interest in this unique syndrome make their consideration difficult

The problems I shall consider are (1) conclusions regarding the pathogenesis, (2) consideration of the conditions that should be included as manifestations of a general disturbance of lipid metabolism, (3) the nature of the nodular lesions and finally, (4) consideration of clinical features in general

CONCLUSIONS REGARDING PATHOGENESIS

All the varied xanthoma manifestations can be brought back to a single pathologic principle the reticulo-endothelial system is infiltrated by certain substances According to this interpretation, the change is essentially chemical Lipoids and, in fact, all sorts of metabolic products, find particularly receptive cells in one part or another of the system, but lipoids, because of their physiochemical nature, are most often observed The idea of an abnormal activity of the system in connection with lipid metabolism is purely speculative The change depends primarily on an increase of lipoids in the body fluids and secondarily on the duration of the condition of the blood and the local blood and lymph supply A rise in the amount of lipoids in the body fluids or an increase through stasis may result in storage, and even after sufficient length of time, when the lipid content of the fluids is so low as to appear normal, the lipophilic substance sometimes comes into view Such factors as trauma and inflammation predispose to storage, and there are, without doubt, other undetermined factors, storage occurs when there is increased activity of the cells Disturbances of circulation of the most varied kinds play a part, as is evidenced by the fact that a reversibility of the process with a decrease in hypercholesterolemia is occasionally observed The tissues are not necessarily injured in becoming the seat of such a storage of fat, unless the secondary reactions in the lesions have already taken place In general, the infiltration depends on the rise in amount of lipid Certain accessory factors predispose to localization, but hyperlipidemia itself suffices to produce lipid storage (xanthoma manifestations)

It is necessary to recognize that even though considerable, hyperlipidemia does not always provoke lipid storage Although this fact does not permit one to doubt the certain rôle of hyperlipidemia, it indicates that there are still unknown elements in the problem

The biologic agents in the taking up of lipid substances are the reticulo-endothelial macrophages The chemical nature of the content of these cells is variable, and the extent of the infiltration differs in

each case. When it is more in the skin, it is less evident in the internal organs and vice versa, or even when more in one organ, it is less in another.

One can assume that, depending on the reactive state of the individual, the reticulo-endothelial macrophages appear at one time as an actively evolving diffuse process, and at another, grouped in the form of slowly developing nodular growths. The behavior of excess lipoids circulating in the body fluids recalls in many ways a relationship to other metabolic processes. The comparison with gout caused by uric acid and gout caused by calcium is suggestive.

CONDITIONS THAT SHOULD BE INCLUDED AS MANIFESTATIONS OF A GENERAL DISTURBANCE OF LIPOID METABOLISM

A review of the literature shows that there is no agreement as to what conditions should be included as the manifestations of a general disturbance of lipoid metabolism. The cases of xanthoma of the eyelid are separated from the multiplex group. The cases of glycosuria are considered by themselves, the tuberous and tendon sheath varieties are sometimes studied in connection with dermatologic investigation, and again as unrelated conditions in surgical or pathologic literature. Those developing before puberty are separated from cases developing at a later period, and the generalized forms are frequently described as separate conditions.

According to several investigators, however, there is no essential difference between xanthelasma palpebrarum, xanthoma multiplex and generalized xanthoma, and Niemann's disease and Gaucher's disease are regarded as related conditions.

The relatively large series of cases here described in which hyperplasia of the lipoid cells was present, both in the inner organs and as localized nodular lesions arising from white fibrous connective tissue, makes it possible to consider them as a sort of connecting link which unites these different forms.

Clinical observations as well as microscopic changes appear to justify the consideration of Niemann's disease as the widespread, rapidly developing infantile type of this disturbance of lipoid metabolism. It is possible that with further knowledge concerning lipoid metabolism and its relation to general metabolism, Gaucher's disease may also be included in this grouping. Its similarity to Christian's syndrome supports this view. Gaucher's disease appears to be the same condition infiltrated with more complex lipoproteins.

In regard to cases associated with icterus and diseases of the liver and certain diseases of the kidney, this study suggests that these symptoms may be secondary to the lipoid hyperplasia and also represent the manifestations of a primary disturbance of lipoid metabolism. The

cases showing glycosuria and diabetes mellitus fall into the same grouping only modified by the associated disturbance of carbohydrate metabolism. It may be that the disturbance in carbohydrate metabolism, in such cases, results from the hyperplasia of the lipid cells. It has repeatedly been observed that diabetes mellitus is invariably associated with a disturbance of fatty metabolism and that glycosuria has sometimes been known to appear after, as well as before, the occurrence of the xanthoma manifestations.

These observations indicate that there are still other conditions that can be brought into this relationship—at least some of the group now classed as multiple myeloma and a scattered series of cases, unidentified as to etiology, which have been described in the literature.

The clinical manifestations, the microscopic changes and the chemical content of the lesions show great variations, but all these conditions represent the same irritative proliferation of connective tissue elements (i.e., reticulo-endothelial hyperplasia resulting from the infiltration of lipoids), their only difference being in the nature of the lipoids concerned. The manifestations vary in clinical form according to the rate of development, the duration of the process and the age of occurrence.

The clinical conditions which can be brought together as primary disturbances in lipid storage of the reticulo-endothelial system are

Xanthelasma palpebrarum, a slowly developing form usually occurring in adults.

Xanthoma multiplex and its varieties representing a more acute process occurring frequently in early childhood.

So-called *xantho-myeloma* of the tendon sheaths occurring at all ages but usually in young adults.

Generalized visceral xanthoma-xanthomatosis, including Christian's syndrome, occurring especially in early childhood.

Niemann's disease, the rapidly developing generalized form, in infancy.

Xanthoma diabeticorum, a form modified by a disturbance of carbohydrate metabolism, in which the disturbed carbohydrate metabolism may prove to be secondary to the hyperplasia of the lipid cells.

Gaucher's disease, perhaps modified by a disturbance of protein metabolism, in which case the disturbed protein metabolism may also prove to be secondary.

Concerning the cases now classed with multiple myeloma and certain unidentified cases scattered through the literature, further study would be necessary to determine which of these should be included in this group.

THE NATURE OF THE NODULAR LESIONS

In this syndrome the lesions that are most notable morphologically are the yellow to yellowish brown nodular lesions. In the fourteen cases here described, these tumor-like forms were numerous, appearing to arise from the white fibrous connective tissue of the dura, peri-

osteum, peritoneum and pleura, and rarely in the interstitial tissue of certain organs. The histologic examination showed that they were characterized by the presence of lipoid-containing cells and great variability in structure. In one part, they had angiomatous characteristics, in another, they gave the appearance of a fibroma, and through extensive differentiation seemed to suggest a granuloma form, frequently, the picture gave the impression of true mesenchymal giant cell sarcoma.

Various significances have been suggested for these nodular lesions. They have been regarded as tumors of the connective tissue, secondarily infiltrated with lipoids, as special tumors developing from xanthoma cells, as granulomas developing from the occurrence of an inflammation of undetermined nature, having provoked the local fixation of the excessive lipoids circulating in the blood, or as granulomas which have become xanthelasmic as a result of a degenerative process and which have liberated the constitutional cholesterol locally.

As recently as 1924, in discussing the autopsy of the patient originally described by Griffith, Wiedman and Freeman stated that "the presence of 'xanthomas' (nodular lesions) in the viscera in this case is to be accounted for on the basis of coincidence, one moiety being a granuloma of an undiagnosed disease, and the other the result of hypercholesterolemia."

The constant symptoms in this series of cases indicate that all the different lesions, diffuse and nodular, are a part of the same pathologic process. They have a common etiology—hyperlipoidemia.

In spite of the fact that the nodular lesions, by their size and tissue structure, frequently give the impression of true neoplasms and sometimes of tumors of the granulation tissue, they are not real tumors. Their distribution does not necessarily correspond with hematogenous metastases, and their lack of an infiltrative destructive character, shown by their avoidance of vital tissue, distinguishes them from the true neoplasms. Their long continuance of development, suggestively symmetrical distribution and occasional retrogression indicate a systemic process rather than an autonomous growth.

To understand the nature of these tumor-like nodules, one must consider them from their clinical and developmental side as well as from their histologic structure. If one takes into account their relationship to the reticulo-endothelial system, the process is made clear and their development may be summed up in the following manner. The constant presence of ("foreign body") excess lipoids in the blood stream causes an irritation of the vessel walls, whereupon a perivascular cell infiltration takes place. At first, small round lymphoid cells with little protoplasm appear, then, by splitting of the vessel walls, fusiform cells with an abundance of protoplasm develop, and finally, owing to

fusion, multinuclear xanthoma cells are formed. These cells show a common vessel endothelial origin and all contain lipoids, the older and more mature cells containing the greater amount. They vary in form and size, but their nuclear structure is similar and they never show karyokinesis. The youngest cells are always in the center of the lesions near the blood vessels and the older and more mature xanthoma cells nearer the periphery.

The cells of the reticulo-endothelial system are in constant renovation which is stimulated by "blockage", that is, when the cells are loaded with a given substance they become refractory to all other substances and so stimulate the demand for more cells (Kiyono). The nodular lesions under consideration are the result of perpetual blockage. The histiocytes, being immediately filled by lipid from the body fluids, become refractory to all other substances and so stimulate the demand for more cells, which in their turn become loaded, and repeat the process provoking the continuous increase in the new formation. Thus, the xanthoma nodule does not increase by multiplication of its cell elements, but by the addition of new cells.

The characteristic xanthoma cells are not always observable in the lesions. This and the fact that the lesions sometimes retrogress or recur after excision is explained by their biologic nature. One is not dealing with true neoplasms, but with hyperplastic new formations, i.e., lipid storage tumors. The formation of these nodules is a compensatory act on the part of the body in its attempt to rid the blood of an excess of lipid which cannot be properly excreted.

These views, confirmed by the experimentation of Anitschkow and Kuczynski and by the studies of microscopic changes by Wustmann and Weber and others, are of interest clinically as they bring into relationship with this pathogenesis a long series of, perhaps rare, new formations arising from the dura, periosteum, pleura, pericardium, peritoneum and endosteum, as well as from the tendinous, peritendinous and periarticular surfaces and fascia. To the clinician this is important as it decides their benignancy or malignancy and so determines the manner of treatment. Broders, in describing the latter group under the title "Benign Xanthic Extra-Periosteal Tumors of the Extremities Containing Foreign-Body Giant Cells," remarked that they masquerade under various names—sarcoma, myeloid sarcoma, myeloid endothelioma, myeloxanthoma, granuloma, giant cell tumor and giant cell sarcoma.

The bone destruction associated with these nodular lesions, in the cases I have described, is a notable clinical feature. In every instance the cranial bones had suffered the most, but the roentgen-ray studies demonstrated similar, though less extensive, defects in the flat bones of the pelvis, rarely the scapulae, ribs and vertebrae, and in one instance,

in the femur and humerus. Usually, thickening or evidence of bone regeneration were not found. The bony structure adjacent to the defect appeared normal, according to the x-ray studies, as did all the other bones in the body. One of Schuller's cases showed a lessening of bone destruction and improvement in the general condition. In case 2 of my own, the roentgenograms showed a surprising decrease in bone destruction (compare *C* and *E* in figure 10).

The presence of true foreign-body giant cells in the lesions, in association with pressure, suggests an explanation for this bone destruction. Such changes have been observed in other types of xanthoma by MacLeod, Merrill and Broders. It also occurs in other pathologic conditions in which there are foreign-body giant cells.

An early symptom observed in the majority of these cases was an irritated condition of the gums and a loosening of the teeth. This was usually first indicated by the loosening of the back molars of either jaw. The teeth themselves appeared normal, except for the erosion of some of the cusps, which was similar to the destruction that takes place in the bones. This condition resulted from the xanthoma nodules arising from the periosteum covering the maxillary bones. There were many foreign-body giant cells in these tumor-like masses with the same bone destruction evident. These lesions are of interest in connection with the study of giant cell epulis of the jaw and its etiologic relationship to xanthoma.

The extent of this paper does not permit me to discuss further this problem in which there is so much interest at present, but I wish to repeat that these new formations should be considered from the standpoint of their development, as well as from their pathologic structure. This study indicates that certain yellow to brown, lipid-containing, so-called endotheliomas, angiomas and giant cell fibrosarcomas of the dura, periosteum, pleura and peritoneum are hyperplastic new formations. The lipid in these nodules suggests the irritant which produces them, and so separates them from the field of true autonomous growths.

Local liberation of lipoids can cause the formation of cholesterol granulomas. Various inflammatory and suppurative processes, as well as mesenchymal tumors, can complicate themselves by secondary lipid infiltration. The tumor-like lesions I have described I regard as due, primarily, to a disturbance of lipid metabolism. The fact that the nodules sometimes occur singly does not necessarily separate them from the generalized group, but it indicates that there may be secondary factors, such as trauma, irritation or infection, which determine their localization. Wustmann spoke of these single forms as "storage organs." According to this view, the essential factor in their production is also the excess of lipoids in the body fluids.

CLINICAL FEATURES IN GENERAL

The fourteen cases I have considered all occurred in early childhood. Six of the patients were girls and eight were boys. In ten cases, the probable onset occurred during the second year of life, with one each in the third, fourth, sixth and seventh year. The onset was insidious and periodic, so that in most instances the disease was quite advanced before a physician was consulted.

The family histories, so far as they were studied, did not show any unusual features, with the exception of that in case 2, in which one brother had chronic valvular disease and the mother hypercholesterinemia. The obstetric histories were normal and the births uneventful. During the first year, nutritional disturbances did not occur and development was normal. The blood Wassermann reactions were negative, and tuberculosis was not present. One of the common infectious diseases which frequently occur at this age—measles, mumps, whooping-cough or scarlet fever—antedated the onset in most instances. In both of my cases, a history of trauma was associated with some of the bone defects. It was also mentioned in one of Schuller's cases.

The symptoms depended on the location of the lesions, the extent of involvement and the mechanical effects resulting from pressure and bone destruction. A notable lack of subjective symptoms was apparent, but during the active stage there was frequently increased irritability and often tenderness and pain referred to the lesions.

The occurrence of diabetes insipidus in all of the series, except in one of Hand's patients and in one of my own, is perhaps the most notable clinical feature of the group. In reviewing the literature I have been able to collect reports of eighteen cases of xanthoma, including those I have reviewed, in which there were lesions at the base of the brain surrounding the hypophysis and occasionally involving the posterior lobe of the pituitary, with symptoms of polyuria and polydipsia. The problem which this suggests, as well as various other questions, must remain for further study. But, according to my present belief, these pathologic changes do not determine whether diabetes insipidus is due to pressure and irritation at the base of the brain, or to lesions involving the posterior lobe of the pituitary but, rather, that it may be due to either cause.

It is of interest to note that in case 1 the roentgenogram showed extensive destruction at the base of the brain involving the sella turcica, and that at autopsy yellow masses were found, filling the sella and surrounding the hypophysis. In this case symptoms suggesting diabetes insipidus had not developed. This is surprising when one considers the extent of the nodular lesions, but suggests that the bone erosion may account for the lack of pressure symptoms. If the dia-

betes insipidus is due to pressure at the base of the brain, which is the most commonly attributed cause, it would account for the intermittence of these symptoms and explains why, as in case 1, polyuria and polydipsia do not always develop in the presence of extensive local changes

While instances of diabetes mellitus were not found in the series, the case reported by Fahr and Stamm was regarded as an atypical diabetes mellitus and the patient had intermittent glycosuria. I believe that the condition is closely related to this group and that the patient probably had diabetes insipidus. A clinical relationship between diabetes insipidus and diabetes mellitus has long been observed. This again suggests that the diabetes mellitus in these cases may be secondary to the lipoid hyperplasia or to the resulting lipoid changes in the reticulo-endothelial portion of the pancreas (and possibly other glands)

Retardation in growth was apparent in most instances from the onset of active symptoms. In case 2 normal growth returned with general improvement. In the two older members of the group (see cases reported by Schuller and Kyrklund), besides dwarfism, a typical dystrophia adiposogenitalis developed. They were both active progressive cases. Kyrklund's patient also showed retardation in mental development, as did most of the cases in the infantile group first described by Niemann, and many of those classed as Gaucher's disease. It is a question whether this far reaching process, which involves the reticulo-endothelial system, is not in some way causally related to the mental retardation as well as to the retardation in growth.

Because of the retardation in growth and the diabetes insipidus, Christian and Schuller regarded the "syndrome" as probably due to a disturbance of pituitary function. Various observers explain disturbances of lipoid metabolism as a function of certain endocrine glands (Goldzieher and Hirschhorn). I believe this study suggests that the metabolic disturbance is primary and that the lipoid infiltration in these glands, the pressure effects from the nodular lesions or unknown factors (possibly blockage by lipoids and other pathologic metabolites) definitely related to the pathologic condition account for their disturbed function, that is, the pathologic changes in these cases indicate that the abnormal hormone action is sometimes secondary to the cellular hyperplasia in the glands. This view is directly opposite to the one generally expressed and is suggestive in regard to the part cellular reactions of the reticulo-endothelial system may play in other so-called endocrine disturbances.

A chronic otorrhea occurred in case 1, evidently from involvement of the mastoids by this process. The same condition occurred in several other cases in the series in which mastoid operations were per-

formed. In two instances there was involvement of some of the nasal sinuses, which suggested a rare and new pathologic change for these conditions.

The varying degrees of exophthalmos, which occurred in every instance, may be explained by the bone destructive process. Possibly the size of the nodular lesions in the orbit was a factor, but these changes did not produce sufficient pressure to cause optic atrophy. The fundi in every patient examined were normal.

Various other well recognized clinical conditions may be explainable on the basis of lipid hyperplasia of the reticulo-endothelial system: atheroma, especially of the valves of the heart and larger vessels, certain types of cirrhosis of the liver, "strawberry gallbladder", occasionally cholelithiasis, certain forms of nephrosis, myelin kidney representing an extreme form, osteitis fibrosa, atherosclerosis, certain familial forms of Dupuytren's contracture and cholesteatoma of the choroid plexus.

Lesions of the skin suggesting xanthoma were not found in any of the group here described, with the exception of Hand's second case which resembles the clinical picture of the eruption of juvenile xanthoma of the rapidly developing congenital type. Thus, the clinical observation made by Lubarsch, that when the eruption occurs more in the inner organs less is found on the skin, held true.

In regard to the blood changes in the syndrome, too few examinations were made for any conclusions to be drawn but the observations are of interest. Manifest lipemia was not observed in any instance. There was usually a slight degree of anemia with a moderate increase in leukocytes, this increase sometimes being due to a large mononuclear excess (histiocytosis). In Christian's case, the leukocyte counts varied from 6,600 to 20,100. In my first case, two leukocyte counts were 17,350 and 17,600, respectively. The differential counts were: polymorphonuclears, 64 per cent, large mononuclears, 32 per cent, small lymphocytes, 4 per cent, and polymorphonuclears, 73 per cent, large mononuclears, 20 per cent, small lymphocytes, 7 per cent.

In the patient of Schultz, Weimble and Puhl, the blood changes were such an outstanding feature that at first they believed they were dealing with a case of anemia pseudo-leukemia infantum (von Jaksch anemia). Evidence of a blood destructive process was not found, but this severe anemia was due to the hyperplasia in the long bones interfering with blood formation. The bone marrow was slightly involved in most of the series, but in this case the involvement was extensive.

The lipid cell hyperplasia of the hematopoietic apparatus suggests problems for future study in connection with the explanation of certain, apparently confusing, blood pictures. In the case just mentioned, it is evident that the anemia varies with the extent of the hyperplasia involving the bone marrow. A leukemia of histiocytic origin could

betes insipidus is due to pressure at the base of the brain, which is the most commonly attributed cause, it would account for the intermittence of these symptoms and explains why, as in case 1, polyuria and polydipsia do not always develop in the presence of extensive local changes

While instances of diabetes mellitus were not found in the series, the case reported by Fahr and Stamm was regarded as an atypical diabetes mellitus and the patient had intermittent glycosuria. I believe that the condition is closely related to this group and that the patient probably had diabetes insipidus. A clinical relationship between diabetes insipidus and diabetes mellitus has long been observed. This again suggests that the diabetes mellitus in these cases may be secondary to the lipid hyperplasia or to the resulting lipid changes in the reticulo-endothelial portion of the pancreas (and possibly other glands)

Retardation in growth was apparent in most instances from the onset of active symptoms. In case 2 normal growth returned with general improvement. In the two older members of the group (see cases reported by Schuller and Kyrklund), besides dwarfism, a typical dystrophia adiposogenitalis developed. They were both active progressive cases. Kyrklund's patient also showed retardation in mental development, as did most of the cases in the infantile group first described by Niemann, and many of those classed as Gaucher's disease. It is a question whether this far reaching process, which involves the reticulo-endothelial system, is not in some way causally related to the mental retardation as well as to the retardation in growth.

Because of the retardation in growth and the diabetes insipidus, Christian and Schuller regarded the "syndrome" as probably due to a disturbance of pituitary function. Various observers explain disturbances of lipid metabolism as a function of certain endocrine glands (Goldzieher and Hirschhorn). I believe this study suggests that the metabolic disturbance is primary and that the lipid infiltration in these glands, the pressure effects from the nodular lesions or unknown factors (possibly blockage by lipoids and other pathologic metabolites) definitely related to the pathologic condition account for their disturbed function, that is, the pathologic changes in these cases indicate that the abnormal hormone action is sometimes secondary to the cellular hyperplasia in the glands. This view is directly opposite to the one generally expressed and is suggestive in regard to the part cellular reactions of the reticulo-endothelial system may play in other so-called endocrine disturbances.

A chronic otorrhea occurred in case 1, evidently from involvement of the mastoids by this process. The same condition occurred in several other cases in the series in which mastoid operations were per-

formed. In two instances there was involvement of some of the nasal sinuses, which suggested a rare and new pathologic change for these conditions.

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also complicate this condition, and these two blood changes might occur at the same time, making the interpretation of the examinations of the blood difficult. Kiyono explained why the histiocytes do not appear more often in the peripheral circulation. The large cells, because of their size, are caught in the pulmonary capillaries and so rarely appear in the peripheral circulation.

Four of the group came to autopsy. In all the fatal cases, there was pulmonitis with an extreme degree of pulmonary fibrosis, which represented a rare type of pathologic change in the lungs. This change is of interest as it suggests the important part played by the lungs in lipid metabolism. Experimentation indicates that the pulmonary tissue is concerned in the destruction of fats. Aschoff regarded the lungs as a sort of digesting organ for lipoids and fats. It may be that the pathologic change causing a stasis of lipoids, as Lubarsch suggested, is a factor in determining the clinical form the group presents, it certainly is a deciding factor in the prognosis.

In the group described there have been seven deaths, and so far as is known, the remaining seven patients are still living. Two, at least, have shown improvement, indicating that the prognosis is better than the clinical symptoms would seem to suggest.

The tentative diagnosis, in most instances, was some form of tumor of the brain, but without exception there was an entire absence of neurologic symptoms or signs suggesting cerebral pressure. It is of clinical interest to remember that the nodular lesions arising from the dura and periosteum with erosion of the bone do not usually cause pressure symptoms. The rarely occurring cutaneous lesions in the generalized visceral forms have the same diagnostic significance as tophi in gout. A yellow coloration of the skin, frequently present in this condition, would also be of diagnostic importance. The varying degrees of exophthalmos and the noticeable tendency to dwarfism give most of these children a facies and "froglike" appearance which is nearly typical of the condition.

There should not be any difficulty in the clinical diagnosis of the syndrome. In any case of bone defects, especially of the cranium, polyuria, polydipsia, exophthalmos, even of loose teeth, dwarfism and dystrophia adiposogenitalis, this condition of disturbed lipid metabolism should be considered. It is important to remember that the blood serum does not always show an increase in lipoids and that various kinds of lipoids are concerned in this process.

Regarding treatment, the pathogenesis of hyperlipoidemia suggests possibilities of rational procedure to the internist. It is generally agreed that hyperlipoidemia can be produced by types of nourishment. Animal experimentation shows that the cholesterol content of the blood is easily influenced by the cholesterol content of the food. While the

juvenile form I have described is frequently regarded as idiopathic, this view is theoretical. From the clinical standpoint, it appears permissible to consider this metabolic disturbance as in the nature of a diet disease—not a deficiency disease, but rather the result of certain kinds of food excess. “Excess of albumins, as well as of lipid-containing foods, brings forth a true lipid reaction” (Aschoff). It is also evident that infections and toxic states aggravate the condition (Fahr).

This view brings a long series of pathologic conditions into the realm of internal medicine. According to Rothschild and Rosenthal, the dietetic treatment of persons with hypercholesterolemia consists in diminishing the intake by using foods of low cholesterol content and by rendering absorption as difficult as possible. A diet low in fat content they believed answers both purposes. In cholelithiasis, they have found effective the giving of a fat-free diet for three or four days, alternating this with a more liberal but low fat diet.

In case 2 with restriction in lipid-containing foods, a diet consisting of a moderate amount of protein and green vegetables, and the giving of desiccated thyroid and anterior lobe pituitary by mouth, along with intelligent hygienic care and dental prophylaxis, the blood cholesterol has decreased from 317 mg per hundred cubic centimeters in 1926 to 111 mg in 1927. Coincident with this change, there has been a remarkable improvement in the general condition, a return to a normal rate of growth, a lessening in the polyuria and polydipsia and a notable decrease in the bone destructive process, as shown by the roentgen-ray studies. The symptoms in this single case, however, are only regarded as suggestive.

For a long time it has been observed that persons with xanthoma diabeticorum respond to dietetic treatment and recently that the condition is still more promptly influenced by the use of insulin. Some observers have not found insulin generally effective in the group I have described (Ingram), but one can feel hopeful that a successful dietetic rationale will be devised for this (diet) disease.

SUMMARY AND CONCLUSIONS

Two new cases of the striking syndrome “defects in membranous bones, exophthalmos and diabetes insipidus,” one in which a study was made at necropsy, the other in which the patient is still under clinical observation and shows a remarkable improvement in general condition, are here reported and discussed with twelve other reports of cases collected from the literature.

These fourteen cases, all occurring in early childhood, have been brought into relationship with other similar cases already recognized as xanthoma. In this study the clinical picture, the microscopic changes and the pathogenesis have been considered, and their relation to the reticulo-endothelial system has been discussed.

All these cases represent a form of generalized visceral xanthoma-xanthomatosis in which many parts of the reticulo-endothelial system show lipid storage or lipid cell hyperplasia. This occurs as a diffuse process in the interstitial cells of various organs, especially the lungs, liver, lymph nodes, bone marrow and spleen, as well as in hyperplastic nodules arising from the areolar tissue, particularly of the dura, periosteum, pleura and peritoneum. This pathologic change, diffuse and nodular, is regarded as the manifestation of a disturbance of lipid metabolism.

Although with the present limited knowledge of lipid metabolism and its relation to general metabolism positive deductions cannot be drawn, the consideration of these cases in connection with facts already in the literature, especially the part played by the reticulo-endothelial system, seems to justify certain general conclusions.

According to my present interpretation of this process, lipid and various other substances in excess in the body fluids become pathogenic for the organism. There is at first an irritation of the vessel walls, then perivascular cell infiltration takes place, the lesions increasing as a result of the progressive blockage of the reticulo-endothelial system. This hyperplastic reaction represents a compensatory act on the part of the body and is its attempt to rid its fluids of substances that cannot be properly excreted and that act as irritants. Trauma or inflammation may account for the special localization in these cases or there may be some other factor not as yet determined. It occurs in the places in which there is increased cell activity in the presence of hyperlipidemia.

Abnormal congenital predisposition has usually been ascribed as the cause of the excess lipid in the body fluids, but this has not been proved. Whether this condition represents a congenital or acquired familial or nonfamilial derangement of lipid metabolism must await future study. This condition, however, may prove to be a diet disease in the same sense as are uric acid gout and calcium gout.

As this investigation has been made from the clinical point of view, I shall call special attention to certain features of general medical interest.

The relatively large series of cases here described constitute a group which brings together other lipid metabolic diseases of the reticulo-endothelial system. Niemann's disease is the rapidly developing generalized xanthoma of infancy, while Gaucher's disease represents a similar condition with an infiltration of more complex lipoproteins, and this study suggests that in the cases associated with diabetes mellitus or glycosuria, icterus and disorders of the liver and certain diseases of the kidney, these symptoms are secondary to the lipid cell hyperplasia and are also the result of primary disturbance of lipid metabolism. Each of these conditions differs in clinical form, in the pathologic structure of the lesions, and in the nature of the lipids

concerned, but they all represent the same irritative proliferation of connective tissue elements—reticulo-endothelial hyperplasia, i.e., there is no essential difference between xanthoma in all its many forms, Niemann's disease and Gaucher's disease. They all are manifestations of the same pathologic process, perhaps modified by certain differences in the patient's general metabolic state.

The bone destruction, exophthalmos, diabetes insipidus, dwarfism and infantilism often present and frequently regarded as evidence of disturbed pituitary function are the results of this pathologic change. The same cause can be assigned for the less often observed dystrophia adiposogenitalis, for certain confusing blood pictures and other well recognized conditions.

My conclusion that the pituitary dysfunction results from the lipid cell hyperplasia is suggestive concerning the part various cellular reactions of the reticulo-endothelial system may play in other so-called endocrine diseases. Such a hypothesis gives a definite pathologic-anatomic basis for, and explains the correlation of, certain disorders of the ductless glands.

That the nodular lesions with their varied pathologic changes (sometimes in a late stage of development not even showing foam cells) are hyperplastic new formations gives support to the opinion that a considerable number of yellow to yellowish brown lipid-containing so-called endotheliomas, angiomas, giant cell fibrosarcomas of the dura, periosteum, pleura and peritoneum are not autonomous growths but lipid storage tumors.

The recognition of the fact that the varied symptomatology is caused by the pathologic change resulting from hyperlipoidemia is important, since in this manner can be explained the pathogenesis of a number of other obscure conditions, and methods of treatment for all these conditions are suggested.

Finally, this lipid metabolic disease of the reticulo-endothelial system—lipoid gout—when viewed in all its many forms, is by no means a rare condition.

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SYNOVIAL FLUID IN CHRONIC ARTHRITIS

BACTERIOLOGY AND CYTOLOGY *

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The object of these studies on chronic arthritis has been to correlate the bacteriology and cytology of synovial fluid with the clinical aspects of the disease. The anatomy and physiology of the cellular elements were studied by the supravital method of staining living cells. An endeavor was made to ascertain whether there is any difference between the cytologic observations in sterile synovial fluid and in that from which positive cultures of bacteria are obtained. There is no account in the literature of a correlation of these factors.

Considerable attention has been given in the literature to the bacteriologic and clinical aspects of both acute and chronic arthritis. Cytologic studies of the synovial fluid have been considered in less detail and rather inadequately. We had hoped that this would have some bearing on the cultural observations, and that a positive joint culture could be predicted from the number and types of cells found. Studies of syphilitic, tuberculous, acute septic and traumatic types of arthritis are not reported. The data presented were accumulated by the study of sixty-three cases of chronic arthritis. The cases were seen in the wards and in the outpatient department of the Johns Hopkins Hospital during the years 1926-1927.

CLINICAL STUDY

The cases studied, as determined by clinical and roentgenologic evidence, included fifty-two of the infectious type, nine of the hypertrophic type and two of the infectious and hypertrophic type. These cases presented various degrees of clinical activity, manifested by swelling, tenderness, stiffness and increase in local heat of the joints. There were fifty-four cases of multiple joint involvement, and nine cases of single joint involvement. In the latter group, two patients had localized arthritis in the hip joints, and seven had localized arthritis

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in the knee joints. An analysis of the cases as to sex showed that 54 per cent were in men and 46 per cent were in women. This percentage is essentially the same as that found by Billings, Coleman and Hibbs¹ and by Pemberton and Pierce.² The former, in 411 cases, reported 59 per cent in men, and 41 per cent in women, while the latter reported 700 cases with 69 per cent in men and 31 per cent in women. The patients varied in age from 15 to 72 years. The average age was 43

TABLE 1—*Analysis of Probable Source of Infection in Sixty-Three Cases of Chronic Arthritis*

	Probable Sources of Infection	No. of Cases	Per Cent
1	Throat without history of acute tonsillitis	23	38.9
2	Infected tonsils	14	23.7
3	Prostatitis	7	11.8
4	Infected sinuses	4	6.8
5	Abscessed teeth or pyorrhea	3	5.1
6	Urethritis	3	5.1
7	Gastrointestinal tract	2	3.4
8	Uterine cervicitis	1	1.7
9	Pylitis and cystitis	1	1.7
10	Infected toes	1	1.7

The duration of the disease varied from one month to sixteen years. The average duration was three years.

Particular attention was paid to the probable source of infection. An analysis of the most likely foci of infection in the sixty-three cases is recorded in table 1.

In four of these sixty-three cases the probable sources of infection could not be determined. Two were thought to be partly metabolic in origin. In the nineteen cases in which organisms were grown from the

TABLE 2—*Probable Sources of Infection in Nineteen Cases of Chronic Arthritis in Which Organisms Were Grown from Joints or Regional Lymph Nodes*

	Probable Sources of Infection	No. of Cases	Per Cent
1	Throat without history of acute tonsillitis	8	42.1
2	Infected tonsils	5	26.3
3	Infected sinuses	2	10.5
4	Prostatitis	2	10.5
5	Cervicitis	1	5.3
6	Urethritis	1	5.3

joints or regional lymph nodes, the probable sources of infection were as recorded in table 2.

Reports of these nineteen cases are given at the end of the paper.

1 Billings, F., Coleman, G. H., and Hibbs, W. G. Chronic Infectious Arthritis. Statistical Report with End-Results, J. A. M. A. **78** 1097 (April 15) 1922.

2 Pemberton, R., and Pierce, E. G. Clinical and Statistical Study of Chronic Arthritis Based on 1,100 Cases, Am. J. M. Sc. **173** 31, 1927.

BACTERIOLOGY OF JOINTS AND REGIONAL LYMPH NODES

Schullen,³ in 1893, described a small bacillus which he obtained by culture on gelatin bouillon of joint fluid from patients with chronic rheumatoid arthritis, and which, when injected in dogs, produced arthritis

Blaxall,⁴ in 1896, found in the synovial fluid of rheumatoid arthritic joints, and occasionally in the blood, a minute bacillus. It possessed marked polar staining, was decolorized by Gram's method, and could be stained only by prolonged immersion in aniline-methylene blue. Inoculation experiments failed.

Poynton and Paine,⁵ in 1902, who had previously found a diplococcus or short streptococcus in patients with acute rheumatism, isolated a similar organism from an osteo-arthritic joint, which produced arthritis when injected intravenously into rabbits.

Rosenow,⁶ in 1914, stated that in cases of arthritis deformans he found the same organism in regional lymph nodes as in the joints, but he did not cite any examples. He made cultures of regional lymph nodes in fifty-four cases of chronic arthritis. In thirty-two instances he recovered nonhemolytic streptococci, in fourteen, *B. welchii*, in five, staphylococci, in five, diphtheroids, in three, *B. mucosus*, in one, *Micrococcus catarrhalis*, in one, gonococcus, and in seven, no growth.

Bloomfield,⁷ in 1915, studied the bacterial flora of lymph nodes. He employed in this study seven normal and twenty-five pathologic nodes. In a high percentage of cases, organisms could be grown more often in diseased than in normal nodes. The organisms obtained were saprophytes, identical with, or closely related to, the surface flora of the body. Bloomfield suggested that these organisms constitute, perhaps, a more or less permanent flora of lymph nodes. None of the twenty-five strains isolated could be shown to be the cause of specific diseases.

Billings, Coleman and Hibbs,¹ in 1922, made cultures of regional lymph nodes in twenty-eight cases of chronic infectious arthritis. In one case they isolated a hemolytic streptococcus, nineteen cases showed green, nonhemolytic streptococci, and one revealed a mixture of hemo-

3 Schullen. Untersuchungen über die Ätiologie der sogen. chronisch-rheumatischen Gelenkentzündungen, Berl. klin. Wchnschr. **30** 865, 1893.

4 Blaxall, F. R. Rheumatoid Arthritis. Its Clinical History, Etiology, and Pathology, Lancet **1** 1120, 1896.

5 Poynton, F. J., and Paine, A. Reports of the Pathological Society of London. Brit. M. J. **1** 79, 1902.

6 Rosenow, E. C. The Newer Bacteriology of Various Infections as Determined by Specific Methods, J. A. M. A. **63** 905 (Sept. 12) 1914.

7 Bloomfield, A. L. The Bacterial Flora of Lymphatic Glands, Arch. Int. Med. **16** 197 (Aug.) 1915.

lytic and nonhemolytic streptococci. Joint cultures were made in fourteen cases. In five of these, green nonhemolytic streptococci were cultivated, and in one a mixed hemolytic and nonhemolytic streptococcus growth was obtained.

Boots and Cullen,⁸ in 1922, studied the hydrogen ion concentration of joint exudates in its relation to infection. They found an acid reaction in one case of infection with *Staphylococcus aureus*, and in one case of infection with *Streptococcus hemolyticus*. In cases of rheumatic fever and arthritis of undetermined origin, the p_H of the synovial fluid approximated that of the blood.

Holman⁹ in a recent review, discussed the subject of focal infection and elective localization. Reference should be made to this paper for a more detailed account of the rôle of focal infection in pathologic processes.

All our cultures were made by planting the synovial fluid in blood beef infusion broth at p_H 7.4 and on blood beef infusion agar at p_H 7.4. Deep cultures were made with ascitic fluid dextrose—beef infusion agar, p_H 7.4. Cultures were planted on ascitic fluid dextrose agar, the tops of the latter tubes were heated to force out the oxygen, and a rubber stopper was inserted immediately. Similar procedures were used for lymph node cultures when these were made. Table 3 gives the results in the positive cases.

In all, cultures were made of the joint fluids of sixty-three patients, with the recovery of organisms in fourteen, or 22 per cent. In some of the positive cases repeated punctures and cultures were made, giving a total of twenty-one bacteriologically positive joint fluids. Eleven of the joint cultures contained *Streptococcus viridans*, two gonococci and one *Staphylococcus aureus*.

Regional lymph nodes were excised or punctured, and cultures made in twenty-one of the sixty-three cases.¹⁰ There were ten positive growths or 48 per cent. Of the ten positive growths, nine were of *Streptococcus viridans* and one of gonococcus. In five of these cases, there were positive joint cultures, the same type of organism being grown from the joint and the lymph node.

8 Boots, R. H., and Cullen, G. E. The Hydrogen Ion Concentration of Joint Exudates in Rheumatic Fever and Other Forms of Arthritis, *J. Exper. Med.* **36**: 405, 1922.

9 Holman, W. L. Focal Infection and "Elective Localization," *Arch. Path.* **5**: 68 (Jan.) 1928.

10 For a number of years in the Johns Hopkins Hospital Clinic, lymph nodes have been removed for culture in chronic arthritis. Stimulation for part of this work was obtained from experience with these cultures and contact with Dr. W. S. Baer, Professor of Orthopedic Surgery.

Reference to tables 3 and 4 will show the cell counts in most of the positive cases. The relationship between the increased cell count and the positive cultures is discussed under the heading Cytology.

From these bacteriologic studies, it is apparent that positive cultures can be obtained in joint fluids and regional lymph nodes in a fair per-

TABLE 3—Results of Positive Cultures of Synovial Fluid

Case	Joint	Lymph Node	Organism	Growth	Incubation Period, Days	Degree of Clinical Activity	Probable Focus	Duration of Arthritis, Years
1	Left knee		S viridans	Light	1	++	Throat	2
2	Right knee		S viridans	Light	3	+++	Tonsils	5
3	Left knee		S viridans	Light	3	++++	Tonsils	½
4	Left knee	Right inguinal	S viridans	Light	2	++++	Cervix	10
			S viridans	Light	2			
5	Right knee	Epitrochlear	S viridans	Light	6	+++	Throat	2
			S viridans	Light	6			
6	Right knee		S viridans	Light	1	+++	Prostate	3½
	Right knee		S viridans	Light	1			
	Left knee		S viridans	Light	2			
	Right ankle		S viridans	Light	2			
7		Epitrochlear	S viridans	Light	3	+++	Tonsils	15
	Left knee		S viridans	Light	3			
8		Axillary	Gonococcus	Light	6	++	Prostate	¾
	Left knee		Gonococcus	Light	1			
	Left knee		Gonococcus	Light	2			
	Left knee		Gonococcus	Light	2			
	Left knee		Gonococcus	Light	2			
	Left knee		Gonococcus	Light	2			
9	Right knee	Right inguinal	S viridans	Moderate	3	++++	Tonsils	1
			S viridans	Light	3			
10	Right knee		Gonococcus	Light	2	++	Prostate	1
11	Right hip		Staph aureus	Moderate	2	++	Throat	2
12	Right hip		S viridans	Moderate	3	+	Throat	16
13	Right knee		S viridans	Light	3	++	Throat	1½
14	Left knee		S viridans	Light	1	+	Throat	12
15		Right inguinal	S viridans	Moderate	2	++	Throat	8
16		Right inguinal	S viridans	Light	3	++++	Sinus	6
17		Epitrochlear	S viridans	Light	3	+++	Sinus	1
18		Right cervical	S viridans	Moderate	3	++	Tonsils	3¼
19		Left inguinal	S viridans	Light	6	+	Throat	2½

centage of cases of chronic arthritis of nontuberculous and non-syphilitic origin. It is also apparent that in the positive cases, repeated positive cultures can be obtained from the same or similarly involved joints. The coincidence of isolating the same organism from both the lymph nodes and the joints points toward these organisms as the etiologic agents in the arthritic cases reported.

CYTOLOGY OF SYNOVIAL FLUID

The data reported were accumulated from a study of thirty-three fluids from the knee joints of patients with chronic arthritis

The literature contains but little work of real value on the histology of joint fluid. The textbooks of histology and pathology barely mention the subject. Abadie,¹¹ in 1902, examined the synovial fluid in three cases of chronic arthritis, termed by him "arthropathies tabétiques." He found the red blood cells always in great numbers, comprising from 60 to 80 per cent of the total cells present. Of the other elements, 87 per cent were small lymphocytes, 6 per cent were polymorphonuclears and 7 per cent "great mononuclears," endothelial cells and atypical cells. In two cases of arthritis deformans he found somewhat fewer cells, with 60 per cent red cells, 30 per cent lymphocytes and the remaining 10 per cent mononuclears and endothelial cells, without any polymorphonuclears.

Giffon and Abram,¹² in 1907, described a fluid in a patient with syphilis. There was a polymorphonuclear preponderance which, after treatment, changed to a lymphocytic preponderance.

Singer,¹³ in 1915, found joint fluid in arthritis associated with dysentery to be rich in polymorphonuclear leukocytes and lymphocytes.

Cecil,¹⁴ in 1916, studied the pathology of joints and synovial fluid by injecting one or more doses of *Streptococcus viridans* into vitally stained rabbits. Acute or subacute infectious arthritis was produced in many cases. He stated that the joint sections showed a considerable number of large endothelial cells or macrophages in addition to numerous leukocytes. These macrophages, he believed, migrated from the tissue into the joint exudate and could not be seen to develop from the endothelial lining of the joint.

Labor and von Balogh,¹⁵ in 1919, found cells in various arthritides as follows

- (a) Normal knee joint—from 10 to 20 cells per cubic millimeter, no wandering or endothelial cells

11 Abadie, M. J. Examen cytologique du liquide articulaire de quelques arthropathies chroniques, *Compt rend Soc de biol*, 1902, p 945

12 Giffon, V., and Abram, P. L'hydarthrose de la syphilis secondaire. Etude cytologique et experimental de l'épanchement, cited in *Ann d mal vén* 2 53, 1907

13 Singer, G. Erfahrungen aus der letzten Dysenterieepidemie, *Munchen med Wchnschr* 62 183, 1915

14 Cecil, R. L. A Study of Experimental Non-Hemolytic *Streptococcus* Lesions in Vitally Stained Rabbits, *J Exper Med* 24 739, 1916

15 Labor, M., and von Balogh, E. Zytologische und serologische Untersuchungen der Synovia im besonderen bei akuten Gelenksentzündungen, *Wien klin Wchnschr* 32 535, 1919

- (b) Acute rheumatism—always about 7,000 cells per cubic millimeter, mostly polymorphonuclear elements, with a few mononuclears, and about 3 per cent endothelial cells
- (c) Gonorrheal arthritis—about 16,000 cells per cubic millimeter, endothelial cells entirely absent in the acute stage
- (d) Rheumatoid dysentery—
 - (1) Acute stage—from 2,000 to 5,000 cells per cubic millimeter, polymorphonuclears more numerous than mononuclears, endothelial cells always present, but never more than from 2 to 3 per cent
 - (2) Convalescent stage—from 750 to 1,500 cells per cubic millimeter, lymphocyte number may exceed the polymorphonuclears, endothelial cells increased to from 4 to 5 per cent

Pewny,¹⁶ in 1921, used the cell count of synovial fluid to distinguish between traumatic and tuberculous arthritis. He found that in tuberculous arthritis there were almost always a greater number of leukocytes (approximately 1,000) and fewer red cells than in traumatic arthritis. In the latter cases the white cells numbered from 400 to 600 cells per cubic millimeter.

Chesney, Kemp and Baetjer,¹⁷ in 1926, made a careful study of ten patients all of whom had syphilis and arthritis. Five of these had definite syphilis of the joints. In three early cases they obtained total white cell counts of from 17,000 to 24,000 per cubic millimeter. In two late cases the counts were 2,480 and 1,500. In four of their cases of syphilis of the joints there were high percentages of lymphocytes and mononuclears combined (from 43 to 62 per cent). They did not separate the mononuclear elements.

The studies heretofore reported by various authors have been made from fixed films of the cells. Reports are not available on the character of the living cells in the synovial fluid. The supravital technic of studying living cells provides a means of obtaining more accurate and reliable data on their physiology and histology. By this means one can make observations on the ameboid activity, phagocytic power, behavior to altered environment, fragility, degenerative changes and other characteristics. Thus, information can be obtained concerning the life cycle of the cells.

The usual histologic methods require that the tissues should be subjected to rigorous measures, which not only obscure the physiologic processes of the cells, but also produce false pictures.

¹⁶ Pewny, W. Cytologic Investigations of Tuberculous Effusions of Joints, *Wien klin Wchnschr* 34 22, 1921

¹⁷ Chesney, A. M., Kemp, J. E., and Baetjer, F. H. Experimental Study of Synovial Fluid of Patients with Arthritis and Syphilis, *J Clin Investigation* 3. 131, 1926

The behavior of blood cells toward vital dyes was studied by Rosin and Bibergeil in 1902¹⁸ and in 1904,¹⁹ but it is the work of Evans and Scott,²⁰ Simpson²¹ and Sabin²² which has developed efficiently the so-called supravital technic. A brief description has been published by one of us (Forkner²³) and is repeated here. For more detailed descriptions of the method, reference should be made to the works of the foregoing authors.

A thin film of dye in alcoholic solution is smeared across the surface of a previously cleaned, polished, and warmed glass slide. This is done by dipping the end of another slide, with which the smear is made on the former one into a fresh mixture (10 drops) of equal parts of 0.5 per cent alcoholic solution of neutral red, and a 0.1 per cent alcoholic solution of janus green. Solutions of the dyes are kept on hand, made up in 95 per cent alcohol. The dyes are not mixed until they are ready for use, because a mixture is not a stable preparation. Solutions of varying concentrations should be employed for making the dye films until one has gained proficiency in estimating the optimum concentration desired. Emphasis should be placed on staining the cells as lightly as is consistent to obtain good differentiation of the structures they contain. If the dyes are employed in concentrated solutions, the nuclei will be stained and the cells quickly killed. The glassware must be scrupulously clean, because cells are delicate structures, and any acid, alkali, or the like will injure their membranes, and markedly alter their physiologic behavior.

Janus green and neutral red are relatively nontoxic dyes. The former in dilute concentration is a specific stain for mitochondria, and the latter a specific stain for cytoplasmic structures.

In the study of living blood cells, a freely flowing drop of blood is obtained on the under surface of a coverslip, and allowed to fall gently on the slide prepared with the dye. With blood, the plasma takes up some of the dye, and the cells are bathed in the dilute solution from which they become specifically stained. The same procedure is easily applicable to joint fluid.

18 Rosin, H., and Bibergeil, E. *Ergebnisse vitaler Blutfärbung*, *Deutsche med. Wchnschr.* **27** 41, 1902.

19 Rosin, H., and Bibergeil, E. *Das Verhalten der Leucocytes bei den vitalen Blutfärbung*, *Virchows Arch. f. path. Anat.* **178** 478, 1904.

20 Evans, H. M., and Scott, K. T. *On the Segregation of Macrophage and Fibroblast Cells by Means of Vital Acid Dyes and on the Cause of the Differential Effect of These Substances*, *Anat. Record* **16** 148, 1919.

21 Simpson, M. E. *Vital Staining of Human Blood with Special Reference to the Separation of Monocytes*, *Univ. California Pub. Anat.* **1** 1, 1921.

22 Sabin, F. R. *Studies on Living Human Blood Cells*, *Bull. Johns Hopkins Hosp.* **34** 277, 1923.

23 Forkner, C. E. *Material from Lymph Nodes of Man. Method to Obtain Material by Puncture of Lymph Nodes for Study with Supravital and Fixed Stains*, *Arch. Int. Med.* **40** 532 (Oct.) 1927.

Normal joint fluid is clear, thick and stringy. Pathologic states in which there is an increase in joint fluid and increased cellular content show a decreased viscosity and various degrees of turbidity and yellowish color. Because of these characteristics, the joint fluid, when diluted with acetic acid solution, as in the making of ordinary white blood cell counts, forms a heavy cloud in the pipet, preventing accurate enumeration of the cellular elements. For this reason, the fluid is counted either without dilution, or by dilution with physiologic sodium chloride solution. An ordinary blood counting chamber may be used. Total and differential counts were made in all instances.

The cellular content of the normal and pathologic synovial fluid consists of blood cells and certain tissue cells. Red blood cells are not found in normal fluid, and are rarely present in chronic, non-tuberculous, nonsyphilitic arthritis, except as the result of trauma. All types of white blood cells may be found. Occasional clasmatocytes (macrophages) and synovial mesothelial cells may be seen. The term "mesothelial cell" is used to designate the lining cell of the synovial membrane. It is comparable to the endothelial or epithelial cell of other authors. Table 4 gives, at a glance, the essential characteristics of such cells, when stained by the supravital method with neutral red and janus green.

Table 5 gives the cell counts in the joint fluids of patients with chronic arthritis in which bacterial cultures were positive.

Table 6 gives the cell counts in three cases in which regional lymph node cultures were positive, but in which joint fluids were negative.

Table 7 gives the cell count of the synovial fluid in cases in which both the joint fluid and the lymph nodes were bacteriologically negative.

Table 8 gives the cell count in cases in which the joint fluid was negative and the lymph nodes were not cultured.

The average of all the positive joint fluids is as follows: total white cell count, 11,018, percentage of neutrophils, 61.2, basophils, 0.22, eosinophils, 0.1, monocytes, 15.1, lymphocytes, 19.1, clasmatocytes, 3.22, unclassified, 0.9. On the other hand, the average of all the negative joint fluids is as follows: total white cell count, 5,670, percentage of neutrophils, 50.1, basophils, 0.29, eosinophils, 0.17, monocytes, 19.78, lymphocytes, 26.28, clasmatocytes, 2.59, mesothelial cells, 0.61, unclassified, 0.05.

COMMENT

Study of the tables reveals several interesting observations. 1 Both the highest and lowest total number of cells were encountered in the joint fluids from which positive cultures were obtained. 2 The synovial fluids in all the cases studied invariably had an increased white cell count. 3 The average total white cell count of the bacteriologically

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Commercial Fluid, Stained with Neutral Red and

	Polymorphonuclear Neutrophils	Polymorphonuclear Eosinophils	Monocytes	Lymphocytes	Macrophages
Size	Approximately 16 to 20 microns	Approximately 16 to 20 microns	Approximately 10 to 22 microns	Approximately 5 to 20 microns	Approximately 12 to 30 microns
Motility	Active, streaming of granules, nucleus in rear of cell, some nonmotile cells	Slightly active, same type as neutrophil	Moderately active, nucleus remains near center of cell	Moderately active, nucleus in front of cell	Not motile, cells are probably degenerating
Phagocytosis	Rarely phagocytic	Rarely phagocytic	Phagocytic	Little phagocytosis	Moderately phagocytic
Nucleus	Occasionally contain ingested material	Polymorphonuclear	Round, indented, kidney or horse shoe shape	Round, oval or indented	Round or oval
Cytoplasm	Well filled with specific granules	Well filled with specific granules	Gray, appearance like ground glass, containing vacuoles and mitochondria	Filled with debris and ingested cells	May have few refractive neutral red bodies, cytoplasm has grayish granular appearance
Specific granules	Bright, refractive, and only slightly stained, yellowish tinge	Deep red, slightly less refractive than neutrophil granules, even in size	From 25 to innumerable red-brown, non-refractive bodies, with occasional large brown refractive body, uneven in size, may be clustered around centered sphere or scattered through cytoplasm	From 1 to 10 refractive bodies of various sizes, often redder and more refractive than those of monocyte	Occasional refractive, reddish body
Segregation bodies or vacuoles* (red, brown, yellow)	From 0 to 10 red bodies among the bright refractive, specific granules of the cytoplasm	Occasional red vacuole	Numerous, usually perinuclear, usually large, rods, dots or filaments	Difficult to demonstrate, may be shown by staining with Janus green alone	Do not stain
Mitochondria (blue to green)	Occasionally seen in clear area of cytoplasm as delicate rods or filaments	Occasionally seen in clear area of cytoplasm as delicate rods or filaments	Numerous, usually perinuclear, usually large, rods, dots or filaments	Difficult to demonstrate, may be shown by staining with Janus green alone	Do not stain

* The term "segregation" is used in vacuoles segregating the dye and concentrating it in vacuoles.

TABLE 7—Cytology of Synovial Fluid of Cases in Which Regional Lymph Nodes and Joint Fluid Were Both Sterile

Case	Total White Cell Count per O Mm	Percentage of Polymorphonuclears					Percentage of					Total Number per O Mm Polymorphonuclears				Total Lym pho cytes	Total Cls mato- cytes	Total Meso- thelial Cells	Total Unsifted Cells	Clinical Activity of Joint	
		Neutro- phils		Baso- phils		Eosino- phils		Lym pho cytes	Clas mato cytes	Meso thelial Cells	Unsifted Cells	Neutro phils	Baso- phils	Eosino phils	Total Mono cytes						
20	18,400	82					7		2				15,088						1,288	368	++
	15,040	63					20		4				9,475						3,008	602	++
21	11,360	58					28		3		1		6,589						3,181	311	++
22	10,210	67					11						6,861						1,126		++
23	1,200	28					46		4				336						552	48	++
23	2,080	80					16		1				1,694						333	21	++
Aver	9,720	63					21.3		2.3												

TABLE 8—Cytology of Synovial Fluid in Which Fluid Was Sterile and Lymph Nodes Were Not Cultured

Case	Total White Cell Count per O Mm	Percentage of Polymorphonuclears					Percentage of					Total Number per O Mm Polymorphonuclears					Total Lym- pho cytes	Total Clas- mato- cytes	Total Meso- thelial Cells	Total Unsifted Cells	Clinical Activity of Joint	
		Neutro phils			Baso phils		Eosino phils		Lym pho cytes	Clas mato cytes	Meso thelial Cells	Unelas- sified Cells	Neutro phils	Baso- phils	Eosino- phils	Total Mono- cytes						
24	25,920		95					4		3				24,024				659	494		33	++
25	16,480		88					2		1				14,502				189	94			++
26	9,140		89		1			6						8,402	94			470				++
27	7,840		85											6,664								++
28	2,950		84					5		1				2,478				148	29			++
29	2,720		27.5					69						748				188				++
30	2,125		63.4		1.3			24		2.5			1.2	1,347	28			1,752				++
31	1,800		20					20						360				187	53			++
32	400		14.7					34						59				1,080				++
33	350							42						59				168		36		++
34	300		12					50						36				175				++
35	300		10					44						30				132				++
36	110		12		4			65						13	4.4	4.4		75	8.8	4.4		++
37	100							40		8				67				31	26			++
38	100							7		23								67				++
Aver	4,729		42.9		0.45			23.2		3				29								+

positive joint fluids was approximately double that of the negative joint fluids. 4 The highest total white cell counts and the highest incidence of positive cultures were found, as a rule, in the fluids of the most clinically active joints. There were exceptions to this rule. 5 The polymorphonuclear neutrophils were 111 per cent higher in the group of positive joints than in the negative joints. The clasmatoocytes were likewise increased in this group. The number of monocytes and lymphocytes was definitely higher in the negative joint fluids than in the positive fluids. 6 Desquamated mesothelial cells are by no means a constant observation in the arthritic joint fluid. When encountered they appear to be degenerating cells, as will be seen in table 4. 7 The average percentage of mononuclear cells in the joint fluids of patients with chronic nonsyphilitic and nontuberculous arthritis is approximately the same as that recorded by Chesney, Kemp and Baetjer¹⁷ in patients with syphilitic joint disease.

X-ray studies were made in this group of cases, but new information could not be reported. A definite relationship did not exist between the x-ray changes and the cytologic evidence. The number and types of cells found cannot be foretold by study of the roentgenograms. Brief x-ray reports are recorded with the case histories.

SUMMARY

1 Bacteriologic and cytologic studies of the synovial fluids in sixty-three cases of chronic, nonsyphilitic and nontuberculous arthritis are reported. The results of lymph node cultures in twenty-one of these cases are recorded.

2 Positive cultures were obtained from the joint fluid in 22 per cent of the total number of cases. Positive growths were obtained in 48 per cent of the lymph nodes cultured.

3 Increased white cell counts in the synovial fluid were found in all cases. The average white cell count in the synovial fluid in the bacteriologically positive cases was approximately double that in the negative cases. The number of polymorphonuclear neutrophils was distinctly higher in the group in which positive cultures were obtained in the joint fluid. The number of monocytes and lymphocytes was definitely higher in the group in which negative cultures were obtained in the joint fluid. Synovial mesothelial cells are not a constant observation in arthritic joint fluid.

4 Case reports are given of patients with positive bacteriologic cultures of synovial fluid and lymph nodes.

REPORT OF CASES

CASE 1—*History*—Miss A. B., aged 52, was seen in the dispensary on March 11, 1927, with the complaint of pain, swelling and stiffness of the knee joints. A diagnosis was made of chronic infectious arthritis. The onset of pain in the

knees, especially the left, had been gradual, having begun two years before. The knees were swollen and stiff, and grating was noted. No other joints were involved.

The patient's health was excellent in general up to that time. Infected teeth were removed one year after the onset. Sore throat and colds occurred frequently. She suffered from chronic constipation. An appendectomy had been performed in 1916. Nocturia had occurred once a night for many years.

Examination—The patient was obese. The blood pressure was 190 systolic and 160 diastolic. The lymph nodes were not enlarged. The tonsils were small, pale and scarred, nothing could be expressed from the crypts. Many teeth were missing, abscesses were not found. The sinuses were clear. The heart and lungs were normal. The abdomen was normal. The joints of the knees showed tenderness, swelling and crepitus. Observations in the pelvis were negative.

Laboratory examinations revealed the following results. The Wassermann reaction was negative. The urine was normal, except for a trace of sugar. X-ray pictures of the left knee showed hypertrophic arthritis. Aspiration was performed on the left knee on March 24, 1927, a few drops of cloudy fluid were removed. Culture showed a light growth of *Streptococcus viridans*. Sufficient fluid for a cell count was not obtained.

CASE 2—History—L. B., a widow, aged 47, was admitted on Jan. 20, 1927, with the complaint of pain, stiffness and swelling of the joints. A diagnosis was made of chronic infectious arthritis of the right knee, hands and spine. She had had recurrent pain and stiffness in the right knee and in the fingers for about seven years. The patient was admitted to the hospital because of abdominal pain due to a properitoneal hernia for which operation was performed. While she was recuperating from the operation, an exacerbation of the arthritis occurred, with pain, stiffness and swelling of the right knee and the hands.

The patient's health had been poor in general. She had had diphtheria, typhoid fever, scarlet fever, malaria, measles and mumps. The appendix had been removed and the gallbladder drained twenty-three years before. Headaches and stiff neck were of frequent occurrence. Sore throat occurred occasionally. She had had pneumonia, pleurisy and influenza. Nocturia had been present for eight years, causing urination from three to five times each night.

Examination—The patient was obese. The blood pressure was 194 systolic and 96 diastolic. Enlargement of the lymph nodes was not observed. The tonsils were moderately enlarged and reddened. Several teeth were missing, a considerable amount of dentistry had been performed. The heart was moderately enlarged, the aortic second sound was accentuated, the peripheral vessels were moderately sclerosed. The lungs were clear. The abdomen was normal, except for a properitoneal hernia. The pelvis contained small hard Bartholin's glands, but was otherwise normal. The right knee showed tenderness, swelling and crepitus, the hands were slightly swollen and stiff, the lumbar spine was slightly tender, and motion was restricted.

Laboratory examination of the blood revealed red cells, 4,944,000, hemoglobin content, 83 per cent (Sahli), white cells, 11,100, polymorphonuclears 66 per cent. The Wassermann reaction was negative. The urine gave negative observations except for faint trace of albumin. An x-ray picture (fig. 1) of the right knee showed infectious arthritis. The exostoses on the tibial spines and on the inner aspects of the femoral condyles should be noted in figure 1. There was an irregularity about the external condyle of the tibia, and a moder-

ate amount of bone atrophy By aspiration of the right knee on May 5, 1927, a few cubic centimeters of normal fluid were obtained Culture showed a light growth of *S viridans* The cell count was 80 per cubic millimeter The differential count showed neutrophils, 10 per cent, lymphocytes, 50 per cent, and monocytes, 40 per cent

The patient was discharged on May 6, 1927

CASE 3—*History*—E B, a man, aged 37, married, was seen in the dispensary on March 16, 1927, with a complaint of soreness and tenderness of the wrists

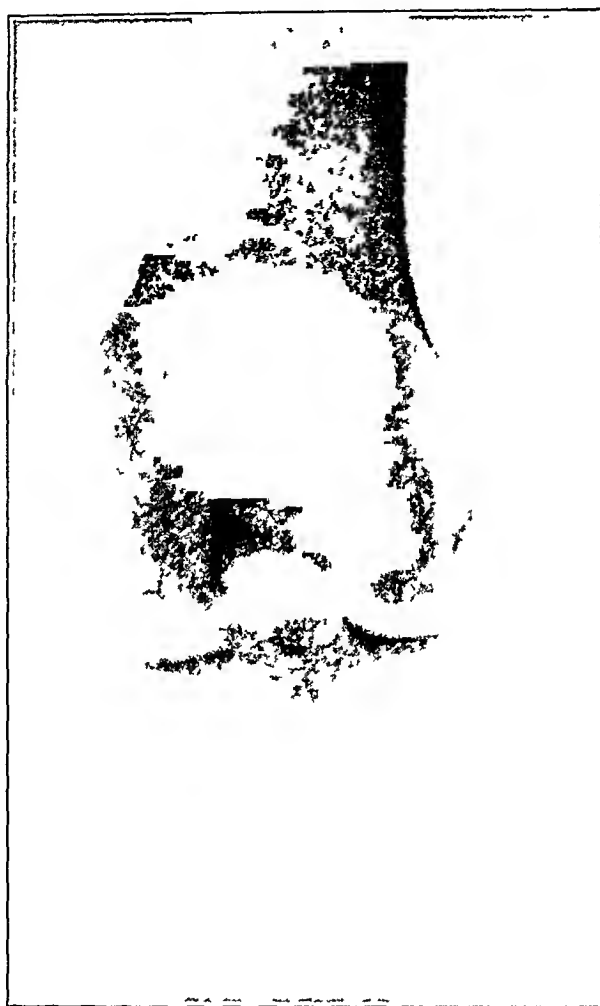


Fig 1 (case 2)—Infectious arthritis of the right knee The exostoses on the tibial spines and on the inner aspects of the femoral condyles should be noted Irregularity is seen about the external condyle of the tibia, and there is a moderate amount of bone atrophy

fingers, knees, ankles and back A diagnosis was made of chronic infectious arthritis Two months previously, the patient had an attack of gummy and tonsillitis Five weeks later, the wrists, elbows, knees and ankles became painful and swollen, this condition persisted The most marked symptoms were in the left knee

The patient's health had been excellent in general He had sore throat frequently as a child, and cold with a cough occasionally A gonorrheal infection was present fifteen years before

Examination—The patient was well nourished and developed. There was a slight enlargement of the lymph nodes. The tonsils were enlarged and showed evidence of chronic infection, there was hypertrophy of the lymphoid tissue in the posterior pharynx. Several teeth were missing, the others were in poor condition, two periapical rarefactions were noted. The heart and lungs were normal. The observations in the abdomen were negative. Enlargement and tenderness were not noted in the prostate. The joints of the fingers were quite sensitive and showed Haygarth's nodes, there was some swelling and tenderness of the wrists, the knees showed slight swelling and tenderness, with evidence of an increase of fluid, the left ankle was extremely swollen and tender, with limitation of motion, the spine was tender in the lumbar region with restriction of motion.

Laboratory examinations revealed the following. X-ray pictures of the left knee showed periarticular swelling. By aspiration of the left knee on March 17, 1927, 3 cc of thick syrupy fluid was obtained. Culture showed a light growth of *S. viridans*. A total cell count was not made because of the scarcity of cells. The differential count revealed neutrophils, 32 per cent, lymphocytes, 18 per cent, and monocytes, 50 per cent.

CASE 4—History—Mrs E F, aged 48, was admitted on July 20, 1927 with the complaint of soreness, stiffness and swelling of the wrists, fingers, shoulders, knees and ankles. A diagnosis was made of chronic infectious arthritis. Swelling and soreness in the ankles was first noted ten years previously, six months later it appeared in the arms and wrists, and still later through her shoulders and knees. This condition became progressively worse.

The patient's health was good in general until that time. Nine years before admission to the hospital a nasal operation was performed, seven years before admission the tonsils were removed. Corneal ulcers occurred about every two years. Constipation was marked. There had been three pregnancies and one miscarriage. A leukorrheal discharge was observed for several years. The patient had lost 16 pounds (7.3 Kg) during the last year.

Examination—The patient was markedly undernourished and in considerable pain. There was a moderate enlargement of the lymph nodes. The tonsils had been cleanly removed. The sinuses were clear. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal, except for slight tenderness in the right upper quadrant. The pelvis revealed marked laceration of the cervix with chronic cervicitis. There was marked swelling of the wrists with deformities of the hands and fingers, the elbows, shoulders, knees and ankles were swollen and tender with limitation of motion, the knees showed evidence of an increase of fluid.

Laboratory examination of the blood revealed red cells, 4,110,000, hemoglobin content, 70 per cent (Sahli), white cells, 9,400, polymorphonuclears, 68 per cent, lymphocytes, 30 per cent, and monocytes, 2 per cent. The Wassermann reactions in the blood and spinal fluid were negative. The urine gave negative observations, except for slight trace of albumin. The x-ray picture of the right knee (fig 2) showed marked infectious arthritis. Marked narrowing of the joint space, atrophy of the bone, irregularity of the external condyle of the femur and the exostoses on the internal condyles of the femur and tibia should be noted in figure 2. Culture of the lymph nodes of the right inguinal group on July 21, 1927 revealed a moderate growth of *S. viridans*. Aspiration of the right knee on July 21, 1927, produced a large amount of turbid fluid. Culture showed *S. viridans*. The cell count was 23,680 per cubic millimeter. The differ-

ential count revealed neutrophils, 93 per cent, lymphocytes, 4 per cent, monocytes, 1 per cent, and macrophages, 2 per cent. Many vacuolated cells were present, the neutrophils were very active.

The patient was discharged on Aug 17, 1927.

CASE 5—History—H F, a man, aged 40, married, was seen in the dispensary on May 24, 1927, with a complaint of swelling, pain and stiffness in the ankles, knees, hips, hands and neck. A diagnosis was made of multiple infectious arthritis. The onset had been gradual eighteen months previously, with pain



Fig 2 (case 4)—Infectious arthritis of the right knee. The knee shows marked involvement. The narrowing of the joint space, atrophy of the bones, irregularity of external condyle of femur and the exostoses on the internal condyles of the femur and tibia should be noted.

in the right hip and knee. At this time, some pain was noted in the right hand with swelling, which became progressively worse. Ten months before admission to the dispensary, further extension occurred to the other joints mentioned.

The patient's health had been excellent. He had sore throat occasionally. All the teeth were out. His appetite was good, and bowel movements were regular. He had not had any venereal disease.

Examination—The patient was poorly nourished. There was a moderate enlargement of the lymph nodes. The tonsils were small, adherent and not

inflamed The sinuses were clear The teeth had all been extracted The heart and lungs were normal The edge of the liver was just palpable The prostate was normal The wrists, fingers, elbows, shoulders and knees all showed tenderness with limitation of motion, there was an increase of fluid in the knees, the hands showed atrophic changes

Laboratory examinations revealed the following results The urine was normal The Wassermann reaction was negative An x-ray picture of the right knee showed periarticular swelling Culture of a lymph node excised from the left epitrochlear showed a light growth of *S viridans* Aspiration of the right knee on June 2, 1927, yielded 50 cc of turbid, straw colored fluid Culture showed a growth of *S viridans* The cell count was 41,920 The differential count revealed neutrophils, 82 per cent, lymphocytes, 11 per cent, and monocytes, 7 per cent Aspiration of the right knee on July 30, 1927, yielded the same type and quantity of fluid as was obtained previously Culture showed *S viridans* The cell count was 39,500 The differential count revealed neutrophils, 89 per cent, eosinophils, 1 per cent, lymphocytes, 6 per cent, and monocytes, 4 per cent

CASE 6—*History*—J G, a man, aged 40, unmarried, was admitted Jan 29, 1927, with the complaint of pain in the back, stiffness in the muscles and neck and soreness all over A diagnosis of chronic infectious arthritis was made The onset occurred about five and one-half years before, with pain in the right hip, the back of the thigh and the right knee This pain was characterized by attacks coming on every few weeks lasting two or three days Four years before admission to the hospital, the stiffness and soreness in the back increased Two and one-half years before admission, he had considerable palpitation and noticed some irregularity of the heart Thirteen months before admission, a tonsillectomy was done and four abscessed teeth were extracted, this was followed by a prompt clearing up of the arthritis One year before admission, he noticed that his right sternoclavicular joint was enlarged During the eight months before admission, many joints were involved but especially those of the dorsal and cervical vertebrae

The patient's health was fair previously He had scarlet fever, measles and pneumonia as a child He had rheumatic fever at the age of 23, and also at 19 Eight years before, he had tonsillitis and quinsy, and during this attack he noticed that his joints were inflamed, particularly in the upper extremities Nine years before, he had influenza and pneumonia Constipation of a moderate degree had been present He had gonorrhea at the ages of 19, 20 and 23 He had lost 20 pounds (9 Kg) during the last year

Examination—The patient was emaciated and apprehensive There were a few palpable lymph nodes in the groins, but no general glandular enlargement A few tonsillar tags remained, culture from throat showed a beta-hemolytic streptococcus Several teeth had been removed, the remaining teeth were in fair condition The blood pressure was 112 systolic, and 62 diastolic There was moderate enlargement of the heart to the left with a systolic murmur at the apex The lungs were clear The abdomen was normal The right lobe of the prostate was moderately enlarged and somewhat thickened, but not tender, the left lobe was slightly enlarged The spine showed considerable stiffness and tenderness, the knees and ankles showed moderate swelling and tenderness, with limitation of motion, the right shoulder showed tenderness, swelling, and limitation of motion, the right sternoclavicular joint was swollen and sore

Laboratory examinations of the blood revealed red cells, 4,000,000, hemoglobin content, 72 per cent (Sahlb), white cells, 10,320, and polymorphonuclears,

70 per cent The Wassermann reaction was negative The urine was clear X-ray pictures of the lumbar spine showed infectious arthritis The right inguinal node was excised and did not show any growth on culture mediums on Feb 9, 1927 A few days after this, there was an acute exacerbation with involvement of almost all the joints, particularly the knees, with marked swelling, redness, pain and stiffness Culture of the blood during this time was positive for *S viridans* on one examination By aspiration of the right knee and ankle on Feb 28, 1927, about 35 cc of cloudy, straw colored fluid was obtained from the knee, and about 5 cc from the ankle Cultures from both fluids showed *S viridans* The cell count was 3,000 The differential count revealed neutrophils, 94 per cent, lymphocytes, 2 per cent, monocytes, 3 per cent, and macrophages, 1 per cent Aspiration of the right knee on March 3, 1927, yielded the same results as were obtained previously Aspiration was performed on the right knee on March 10 and 14, 1927, the culture was negative Aspiration was performed on the right knee on May 18, 1927, the culture showed *S viridans*

The patient was discharged on May 20, 1927

CASE 7—*History*—C K, a man, aged 42, married, was admitted on April 29, 1927, with a complaint of soreness, swelling and stiffness of the joints of the arms and legs, especially in the knees and hands A diagnosis was made of chronic infectious arthritis The onset had been gradual over a period of fifteen years, starting in the fingers of the right hand and spreading to the right wrist and ankles Two and one-half years before admission to the hospital, the back, and then the feet, elbows, shoulders and knees became involved Associated with the pains in the joints he had noticed a loss of weight and appetite with a decrease of strength

His health had been fair He had measles, mumps with orchitis, influenza twice and malaria He had otitis media with drainage at the age of 20 An infection of the sinuses occurred at 16 Tonsillitis and abscessed teeth were not noted Constipation with bilious attacks was frequent Venereal infection had not occurred Nocturia causing urination one or two times each night was present for two years There was occasional pain with micturition

Examination—The patient was rather poorly nourished, with considerable deformity and crippling The blood pressure was 138 systolic and 88 diastolic Marked enlargement of the lymph nodes was noted The tonsils were small, scarred and embedded, but did not appear to be infected The sinuses were clear The teeth appeared to be in fair condition The heart and lungs were normal The abdomen was normal The prostate was slightly enlarged, soft and uniform, and not tender The feet, knees, shoulders, elbows and hands showed swelling, tenderness, crepitus and limitation of motion, the spine was stiff and showed some limitation of motion, the hands showed atrophic changes

Laboratory examinations of the blood revealed red cells, 4,800,000, hemoglobin content, 84 per cent (Sahli), white cells, 6,550, and polymorphonuclears, 69 per cent The Wassermann reaction was negative The urine was normal An x-ray picture of the right hand showed marked infectious arthritis A culture was made of the right inguinal lymph node on April 29, 1927 The growth showed *S viridans* Aspiration of the right knee on April 29, 1927, yielded 50 cc of turbid, straw colored fluid, which gave a positive growth of *S viridans* The cell count was 13,000 The differential count was neutrophils, 49 per cent, lymphocytes, 27 per cent, monocytes, 13 per cent, and macrophages, 11 per cent Aspiration of the right knee on May 3, 1927, yielded the same amount of fluid

as was obtained previously, showing *S viridans*. The cell count was 15,680. The differential count was neutrophils, 42 per cent, lymphocytes, 48 per cent, monocytes, 3 per cent, and macrophages, 7 per cent.

CASE 8—*History*—P L, a man, aged 51, married, was admitted on Dec 15, 1926, with a complaint of pain and swelling of the joints, especially the knees, shoulders and hands. A diagnosis was made of chronic infectious arthritis. The onset had been rather abrupt eight months before with pain through the arches of the feet. After two months, this spread to the left knee, left hip, left hand and practically all the joints. Three months before admission to the hospital, the right jaw became affected. There was considerable pain, swelling and stiffness in the joints.

The patient's health was fair up to that time. He had severe headaches frequently. All the teeth had been out for eighteen years. Bowel movements were fairly regular, and indigestion was not noted. Eight years before admission, he had a gonorrheal infection which subsided, and then he was reinfected. At that time he had a sore heel for a few days which entirely cleared up. He suffered from constipation for fifteen years. Nervous breakdowns occurred fifteen years and one year before admission. He lost 28 pounds (12.7 Kg) during the last six months.

Examination—The patient was somewhat undernourished and had an extremely nervous temperament. There was moderate enlargement of the lymph nodes. The tonsils were scarred, embedded and red, and showed a few whitish areas, indicating a chronic tonsillar infection. Culture revealed a beta-hemolytic streptococcus. An old infection was observed in the left antrum. The x-ray picture was reported to be clear. The teeth had all been extracted. The heart and lungs were normal. The abdomen was normal. The prostate was slightly enlarged with more pus cells than normal. The knees, ankles and hands were swollen and tender, had a limitation of motion and showed crepitus, the hips, elbows and shoulders showed tenderness, crepitus and limitation of motion.

Laboratory examination of the blood revealed red cells, 3,400,000, hemoglobin content, 75 per cent (Sahli), white cells, 7,800, and polymorphonuclears, 72 per cent. The Wassermann reaction was negative. The urine was normal. X-ray pictures of the left foot showed slight infectious arthritis. The lymph node in the left axilla was punctured on Jan 8, 1927. The culture was positive for gonococci. The material withdrawn showed an increased number of neutrophils in the node. Aspiration of the left knee on Jan 14, 1927, yielded a small amount of yellow fluid. The culture was positive for gonococci. The cell count was 3,240 per cubic millimeter. The differential count was neutrophils, 87 per cent, lymphocytes, 5 per cent, and monocytes, 8 per cent. Aspiration was performed on the left knee on Feb 23, March 10 and March 27, gonococci were again recovered in culture.

CASE 9—*History*—Mrs G M, aged 32, was admitted on March 24, 1927, with the complaint of swollen, tender and painful joints. A diagnosis was made of chronic infectious arthritis. The onset had been sudden one year before, with swelling and tenderness in the right knee. The swelling lasted a few days, and then had a tendency to recur repeatedly. Six months later, the left elbow became involved. Three months before admission to the hospital, the toes and knee on the left side were affected, followed by involvement of the right ankle and the left elbow. Recently, the wrists became involved, and in the last two weeks, the jaws and neck.

The patient's health had been excellent. There were many fillings in the teeth. Some constipation was present recently.

Examination—The patient was poorly nourished. Moderate enlargement of the lymph nodes was observed. The tonsils were small and not injected, but they showed a chronic infection. The sinuses were clear. The teeth showed several crowns and one periapical infection. The heart and lungs were normal. The abdomen was normal. The pelvis was free from infection. The knees and ankles showed swelling, tenderness, crepitus, limitation of motion and fluid, the elbows and hands showed swelling, tenderness and limitation of motion, the cervical spine and jaws showed tenderness and limitation of motion.

Laboratory examination of the blood revealed white cells, 8,320, hemoglobin content, 52 per cent (Sahli). A Wassermann test was not done. The urine was normal. An x-ray picture of the right knee showed infectious arthritis. Culture of the right inguinal node excised on March 31, 1927, showed a light growth of *S. viridans*. Aspiration of the right knee on March 31, 1927, yielded a fair amount of slightly turbid, straw colored fluid. The culture showed a moderate growth of *S. viridans*. The cell count was 900 per cubic millimeter. The differential count was neutrophils, 70 per cent, lymphocytes, 8 per cent, monocytes, 8 per cent, macrophages, 4 per cent, degenerating cells, 6 per cent, and unclassified, 2 per cent.

The patient was discharged on April 5, 1927.

CASE 10—History—E M., an unmarried man, aged 22, was seen in the dispensary on Feb 14, 1927, with a complaint of swelling and stiffness of the right knee. A diagnosis was made of chronic synovitis of the right knee. The onset of the condition occurred one year before with pain and swelling of the right knee, associated with slight pain in the left ankle and right thigh. The pain and swelling of the knee persisted. At this time the patient had an acute urethritis.

The patient's health had been excellent. He had an occasional sore throat, and there were a few bad teeth.

Examination—The patient was well nourished and well developed. There was no enlargement of the lymph nodes. The tonsils were enlarged and infected. The teeth showed some devitalization. Epididymitis was present, with chronic tenderness of the ankles.

Laboratory examinations revealed the following results: the Wassermann reaction was negative. X-ray pictures of the right knee showed the bones to be normal, and an increase in fluid. Aspiration of the right knee on Feb 15, 1927, yielded a large amount of turbid, yellow fluid. Culture showed a positive growth of gonococci.

CASE 11—History—Mrs. A N., aged 46, was admitted June 12, 1927, with a complaint of pain and stiffness in the right hip and leg. A diagnosis was made of hypertrophic arthritis of the right hip. The onset occurred two years before at the time of a fall on the right hip which was followed by pain and stiffness in the joint. This became progressively worse, the pain now radiating down the leg. At times the pain became so severe that the patient fell down. Slight pain and stiffness was noted through the left little finger.

The patient's health was excellent. She had sore throat and catarrh occasionally. She suffered from chronic constipation.

Examination—The patient was well nourished. There was no enlargement of the lymph nodes. The tonsils were normal. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal. The pel-

vis was normal. Pain was elicited in the right hip on manipulation, with a limitation of all motion, especially flexion and external rotation.

Laboratory examinations revealed the following results. The Wassermann reaction was negative. The urine was normal. An x-ray picture (fig 3) of the right hip showed hypertrophic arthritis. The marked proliferation of the bone

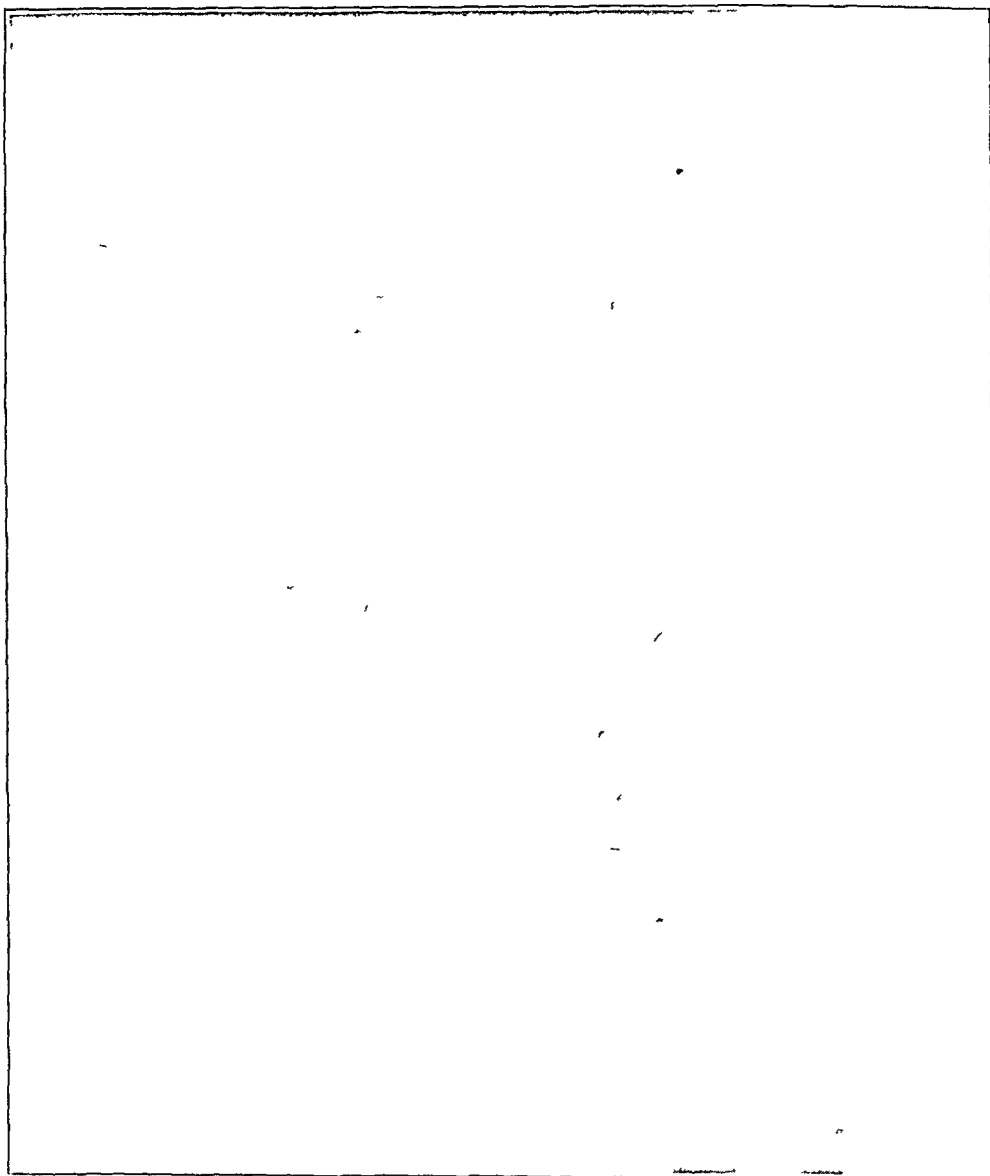


Fig 3 (case 11) —Hypertrophic arthritis of the right hip. The marked proliferation of the bone about the head of the femur and the acetabulum and the flattening of the head, with areas of absorption, should be noted. The joint space is narrowed.

about the head of the femur and the acetabulum and the flattening of the head, with areas of absorption, should be noted. The joint space was narrowed. An arthrotomy of the right hip was performed on June 13, 1927, as the capsule of the joint was opened, a small amount of turbid, yellow fluid exuded. Culture showed a growth of *Staphylococcus aureus*.

CASE 12—History—F N, a man, aged 32, married, was admitted on June 28, 1927, with a complaint of stiffness and pain in the right hip and leg. A diagnosis was made of chronic infectious arthritis of the right hip. For the past sixteen years the patient had recurrent pain and stiffness in the right hip, the pain at times radiated down the leg. About eight months before admission to the hospital, the condition was quite severe, and caused a limping on the right side. Since this time it had gradually subsided.

The patient's health had been excellent. He had colds and sore throat occasionally. Eight years before admission he had a perianal abscess. He denied venereal infection.

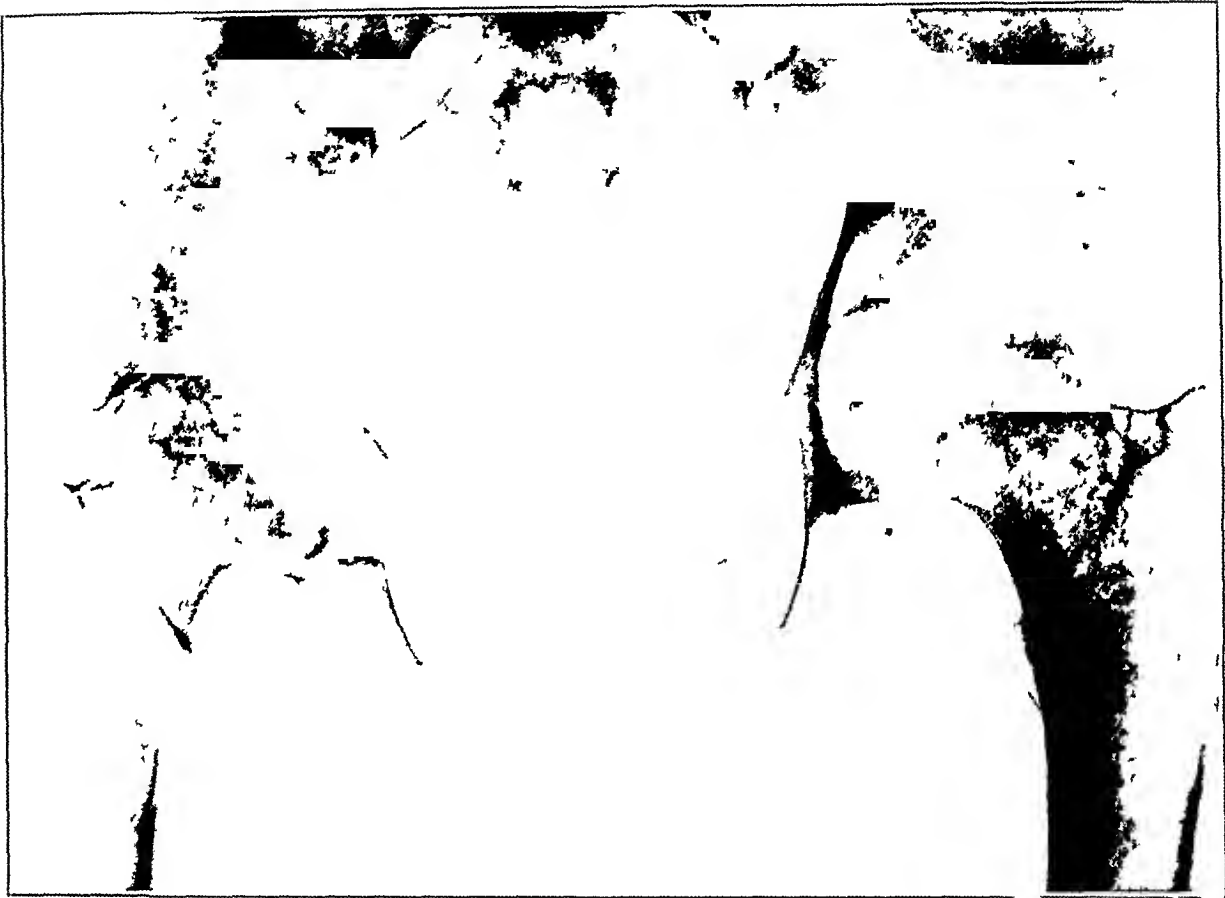


Fig 4 (case 12)—Marked bony destruction of the right hip. There is a flattening of the epiphysis suggesting a gonorrheal or tuberculous infection, not unlike Perthes' disease. Marked narrowing of the joint space. The marked irregularity about the lower articular portion of the head of the femur, and the areas of absorption through the head and that portion of the ilium immediately above the head, should also be noted.

Examination—The patient was well developed and well nourished. Enlargement of the lymph nodes was not noted. The tonsils were small, adherent and not inflamed. The sinuses were clear. The teeth were poorly kept. The heart and lungs were normal. The abdomen was normal. The prostate was normal. The right leg was held in slight abduction and external rotation, there was spasm of the adductor muscles, and limitation of flexion and rotation.

Laboratory examination of the blood revealed white cells, 9,200, hemoglobin content, 85 per cent, lymphocytes, 33 per cent, and monocytes, 1 per cent. The

urine was normal. A Wassermann test was not done. An x-ray picture (fig 4) of the right hip showed a marked bony destruction with a flattening of the epiphysis, suggesting a gonorrheal or tuberculous infection, not unlike Perthes' disease. There was marked narrowing of the joint space. The marked irregularity about the lower articular portion of the head of the femur, and the areas of absorption through the head and that portion of the ileum immediately above the head should also be noted. Arthrotomy was performed on the right hip on June 30, 1927, as the capsule was opened, a large amount of thin, straw colored fluid exuded. Culture from this fluid showed a moderate growth of *S. viridans*.

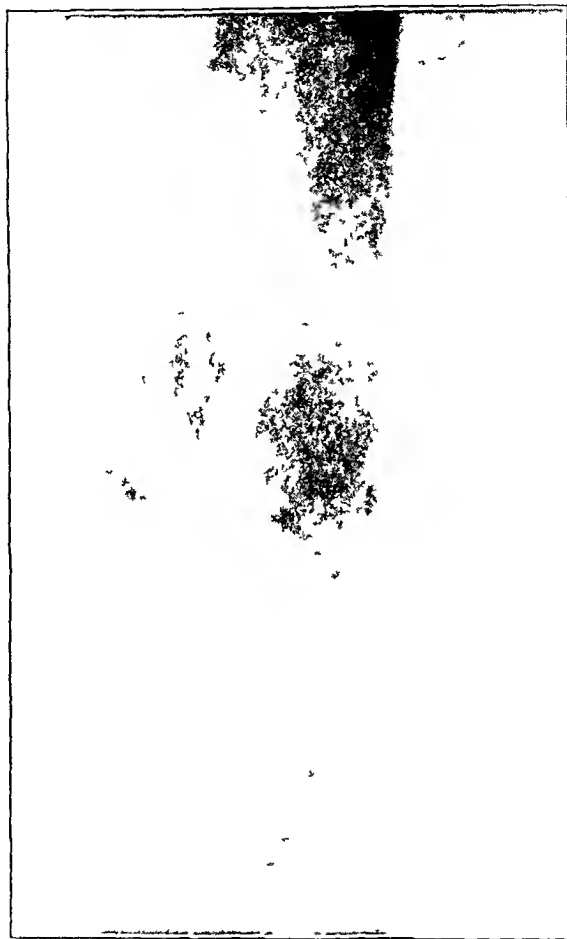


Fig 5 (case 13) —Hypertrophic arthritis of the right knee. The exostoses on the internal condyles of the femur and tibia, with one small loose body opposite, should be noted. Angulation and irregularity are seen about the external condyle of the tibia.

CASE 13—*History*—Mrs. L. P., aged 58, colored, was seen in the dispensary on Jan. 5, 1927, with the complaint of pain, tenderness and swelling of the right knee and fourth toe of the left foot. A diagnosis was made of infectious arthritis of the right knee and left foot. The onset had been gradual, over a period of a year, with pain, swelling and stiffness in the right knee and the fourth left toe. These symptoms had become more acute during the last month.

The patient's health had been fair. She was always subject to headaches. A turbinal was removed fifteen years before. Tonsillectomy was performed thirty

years before. She probably had acute rheumatic fever years previously. She had colds frequently. Some indigestion was noted, but bowel movements were regular.

Examination—The patient was obese and healthy looking, about 30 pounds (136 Kg) overweight. Enlargement of the lymph nodes was not noted. The tonsils had been cleanly removed. The teeth were in fair condition. The heart was slightly enlarged to the left. The lungs were normal. The abdomen was normal. The right knee showed tenderness over the condyles and tuberosities with pain on flexing the joint. Tenderness was felt through the first phalangeal joint of the fourth left toe. The pelvis was normal.

Laboratory examinations revealed the following results. The Wassermann reaction was negative. The urine yielded a slight trace of albumin and sugar. An x-ray picture (fig 5) of the right knee showed hypertrophic arthritis. The exostoses on the internal condyles of the femur and tibia, with one small loose body opposite, should be noted. Angulation and irregularity were seen about the external condyle of the tibia. Aspiration of the right knee on March 1, 1927, yielded a small amount of normal looking joint fluid. Culture showed a growth of *S. viridans*.

CASE 14—*History*—Mrs. M. T., aged 55, was seen in the dispensary on April 20, 1927, with the complaint of pains in the bones and joints of the extremities. A diagnosis was made of chronic infectious arthritis. Twelve years before she had painful, frequent and bloody urine, at that time she first noticed pains in the back and joints. This condition had recurred frequently since the onset, being worse first in one joint and then in the other. At present it was worse in the feet and left arm.

The patient's health had been good. She had typhoid fever thirty years previously. Earache occurred frequently when she was a child. She had sore throat and cold frequently.

Examination—The patient was large, robust and healthy appearing. Enlargement of the lymph nodes was not noted. The tonsils were small, adherent and not inflamed. The teeth were in good condition. The sinuses were clear. The heart and lungs were normal. The abdomen was normal. No focus of infection was found in the pelvis. The left foot and both knees showed swelling, tenderness and crepitation, there was an increase in fluid in the knees.

Laboratory examinations revealed the following results. An x-ray picture of the right knee showed slight infectious arthritis. Aspiration of the left knee on May 5, 1927, yielded 4 cc of thick, stringy fluid. Culture showed a light growth of *S. viridans*. The cell count was 80. The differential count was neutrophils, 15.8 per cent, basophils, 2 per cent, monocytes, 56 per cent, macrophages, 4 per cent, and lymphocytes, 22.2 per cent.

CASE 15—*History*—Miss C. B., aged 24, was admitted on March 24, 1927, with the complaint of swelling of the joints, especially the right knee. A diagnosis was made of chronic infectious arthritis. The onset occurred in 1918, following an attack of influenza, with pain in the right ankle, right hip and right knee. For the last eight years, she had intermittent swelling of the right knee accompanied by pain through her joints. There was only a slight amount of pain and stiffness in the knee. Four years before admission to the hospital, a synovectomy of the right knee was done, this relieved the condition for about one year, but since that time the swelling had been present.

The patient's health had been excellent. The tonsils and adenoids were removed seven years before. One tooth was extracted eight years previously. She had gingivitis in 1920.

Examination—The patient was well developed and well nourished. Moderate enlargement of the lymph nodes was noted. The tonsils had been removed. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal. The pelvis was normal. The right knee was swollen, with some limitation of motion and tenderness.

Laboratory examination of the blood revealed red cells, 4,460,000, hemoglobin content, 82 per cent (Sahli), white cells, 8,400, polymorphonuclears, 74 per cent, and lymphocytes, 26 per cent. The Wassermann reaction was negative. The urine was normal. An x-ray picture of the right knee showed periarticular swelling, with fluid in the joint. The right inguinal gland was excised on March 24, 1927. The culture showed a moderate growth of *S viridans*. A culture of the right knee joint was obtained at arthrotomy on March 24, 1927. On incision of the capsule, a moderate amount of thick, straw colored fluid was obtained. The culture from this was negative.

The patient was discharged on April 6, 1927.

CASE 16—*History*—Mrs. C. B., aged 54, was admitted on March 12, 1927, with the complaint of swollen and painful joints. A diagnosis was made of chronic infectious arthritis. Six years before, the right knee became swollen, contracted and tender. Later, the elbows, wrists and ankles became involved. Two years previously, the process extended to the shoulders and neck. Six months before admission to the hospital, following a series of boils on her right arm, there was some relief from the symptoms in the joints.

The patient's health had been excellent. She had septicemia at the age of 15. Several teeth had been extracted. Iritis, in 1919, cleared up following tonsillectomy performed at that time. Constipation was present. She had cystitis three years before. Hysterectomy was performed sixteen years previously.

Examination—The patient was well developed and well nourished. Moderate enlargement of the lymph nodes was noted. The tonsils had been cleanly removed. There was an infection of both antrums. Examination of the teeth revealed one slight periapical rarefaction. The heart and lungs were normal. The abdomen was normal. Infection was not found in the pelvis. The right hand, right elbow, right knee and shoulders particularly were involved with swelling, tenderness, limitation of motion and crepitus, the left hand, left elbow, left knee and ankles also were involved.

Laboratory examination of the blood revealed red cells, 5,200,000, hemoglobin content, 85 per cent (Sahli), white cells, 9,800, polymorphonuclears, 74 per cent, and lymphocytes, 26 per cent. The Wassermann reaction was negative. A trace of albumin was found in the urine. An x-ray picture of the right knee showed marked infectious arthritis. The right inguinal node was excised on March 14, 1927. The culture showed a light growth of *S viridans*. Aspiration of the right knee on March 14, 1927, yielded about 100 cc of turbid, straw colored fluid. Culture from this was negative. A culture of the right maxillary sinus was positive for *S viridans*.

CASE 17—*History*—Mrs. L. C., aged 34, was admitted on May 8, 1927, with the complaint of swelling and soreness of all joints. A diagnosis was made of chronic infectious arthritis. The onset had been rather gradual, the condition having started two years before with soreness of the right index finger and the thumb. The hand became sore and ached almost constantly. Six months later, the other

hand was similarly involved During the past year, there was an extension of the process to the feet, shoulders, back, hips and elbows, with increasing discomfort She had lost 20 pounds (9 Kg)

The patient's health had been good A tonsillectomy was performed several years previously Many of the teeth were extracted She had two normal deliveries and no miscarriages She had leukorrhea

Examination—The patient was poorly nourished, and was very much depressed Moderate enlargement of the lymph nodes was noted The tonsils had been cleanly removed The sinuses were clear clinically, but the x-ray pictured showed infection of the antrums Many teeth were missing, there was one periapical infection The heart and lungs were normal The abdomen was normal Examination of the pelvis revealed a lacerated cervix and chronic cervicitis The hands and knees were swollen and tender, and had a limitation of motion, the shoulders were tender, with a limitation of motion, the spine was tender, with restricted motion, the hands showed atrophic changes Laboratory examination of the blood revealed red cells, 5,450,000, hemoglobin content, 60 per cent (Sahli), white cells, 8,100, and polymorphonuclears, 50 per cent The Wassermann reaction was negative An occasional faint trace of albumin was observed in the urine X-ray pictures of the hands and knees showed infectious arthritis The right inguinal node was excised on Feb 11, 1927 The culture showed a moderate growth of nonhemolytic streptococci Aspiration of the right knee on May 12, 1927, yielded a small amount of slightly turbid fluid Culture from this did not show any growth The cell count was 5,720 The differential count was neutrophils, 57 per cent, monocytes, 24 per cent, lymphocytes, 17.8 per cent, and macrophages, 1.2 per cent

CASE 18—*History*—A D, a man, aged 53, married, was admitted on March 8, 1927, with the complaint of pain, swelling and deformity of the joints of the hands and knees A diagnosis was made of chronic infectious arthritis The onset followed an acute febrile illness in January, 1924, which was called the grip A few days after this illness pain was felt in the shoulders A cold taken at this time was followed by pain in the shoulders, neck and right elbow The hands became weaker Four months after the onset, the tonsils were removed, resulting in considerable improvement in the arthritis During the last year, the patient was unable to work because of pain and weakness in the shoulders, elbows and hands

The patient's health was excellent He had severe attacks of tonsillitis until the tonsillectomy was performed in 1924 The teeth had given little trouble He had colds frequently He had pleurisy twenty years before He had been troubled a great deal by indigestion There had been occasional palpitation of the heart He had not had any venereal disease Nocturia causing urination from two to three times a night had been present for the last year

Examination—The patient was well developed and well nourished There was moderate enlargement of the lymph nodes, especially in the cervical region The tonsils had been removed, but the pharynx was injected The sinuses appeared clear by the x-ray picture The teeth were in fair condition The lungs were clear The heart was slightly enlarged to the left, without murmurs The abdomen was normal The prostate was not enlarged The hands and knees showed considerable tenderness, swelling and limitation of motion Laboratory examinations of the blood revealed red cells, 4,100,000, hemoglobin content, 80 per cent (Sahli), white cells, 10,000, and polymorphonuclears, 72 per cent The Wassermann reaction was negative The urine was normal X-ray pictures of

the hands showed infectious arthritis. A cervical node was removed on March 24, 1927. The culture showed a moderate growth of *S. viridans*. Aspiration of the left knee on March 14, 1927, yielded fluid small in amount and of normal appearance. The culture was negative. The cell count was 600. The differential count was neutrophils, 34 per cent, monocytes, 18 per cent, lymphocytes, 44 per cent, macrophages, 3 per cent, and mast cells, 1 per cent.

The patient was discharged on April 9, 1927.

CASE 10—History—R. V., a man, aged 62, married, was seen in the dispensary on Oct. 28, 1926, with a complaint of pain and tenderness in the right knee, shoulders, wrists, neck and hands. A diagnosis was made of chronic infectious arthritis. The onset occurred two and one-half years previously, following a trauma of the right knee with the development of pain, swelling, and stiffness. This joint involvement then spread to the shoulders, wrists, neck and hands.

The patient's health was fair. He probably had pulmonary tuberculosis as a child. Twenty-five years before, he had rheumatism in the heels, which spread to the other joints, lasted three weeks and then completely subsided. He had not had sore throat or colds. The teeth were extracted in January, 1925. He had a gonorrheal infection and primary sore twenty-five years previously. He was formerly alcoholic.

Examination—The patient was poorly nourished. Moderate lymph node enlargement was observed. The tonsils were small and not infected. The sinuses were clear. Examination of the teeth revealed sepsis with periapical rarefactions, and pyorrhea. The heart and lungs were normal. The abdomen was normal. The prostate was small, and a focus of infection was not observed. The right knee showed swelling, tenderness, limitation of motion and an increase of fluid, the hands and ankles were swollen and somewhat tender. Laboratory examinations disclosed the following results. The Wassermann reaction was negative. An x-ray picture of the right knee showed infectious arthritis. The right inguinal node was excised on Oct. 28, 1926. Culture from this showed *S. viridans*. Aspiration was performed on the left knee on March 7, 1927, and 5 cc. of normal looking fluid was obtained. The culture was negative. The cell count was 500. The differential count was neutrophils, 82.8 per cent, monocytes, 8.6 per cent, and lymphocytes, 8.6 per cent.

The bacteriologic work reported in this article was done in the laboratory of Dr. Harold L. Amoss, and Dr. J. W. Pierson and Dr. F. O. Coe were consulted in the interpretation of the roentgenograms.

ROENTGEN-RAY THERAPY OF THE HYPOPHYSIS IN A PATIENT WITH ACROMEGALY

ITS EFFECT ON DEXTROSE TOLERANCE *

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AND

H LISSER, M D

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The widespread involvement of various organs and tissues of the body in that remarkable disease, acromegaly, has been commented on by many writers. In a monograph detailing the autopsies in four cases, Cushing and Davidoff¹ emphasized the protean manifestations produced by the exaggerated secretion from the anterior portion of the hypophysis. They called attention not only to the extraordinary osseous deformities and "acromegalic myxedema" which hitherto have dominated the clinical picture but also to the pronounced visceromegalies (cardiac, hepatic, renal, splenic, etc.), and to the noteworthy secondary involvement of most of the other ductless glands.

Several publications of late have dealt particularly with the carbohydrate metabolism in acromegaly (for instance, those of Cushing and Davidoff,² Colwell,³ John⁴ and Ellis⁵). The incidence of diabetes mellitus in acromegaly has been variously estimated from 9 per cent (Arnold⁶) to as high as 40 per cent (Borchardt⁷). Cushing and Davidoff² reported glycosuria one out of four times (25 per cent) in

* From the Endocrine and Metabolic Clinics of the University of California Medical School

1 Cushing, Harvey, and Davidoff, L. M. Studies in Acromegaly. V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph 22, Rockefeller Inst. M. Research, 1927

2 Cushing, Harvey, and Davidoff, L. M. Studies in Acromegaly. VI. The Disturbances of Carbohydrate Metabolism, Arch. Int. Med. **39** 751 (June) 1927

3 Colwell, A. R. The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1, 1927

4 John, H. J. Spontaneous Disappearance of Diabetes, J. A. M. A. **85** 1629 (Nov. 21) 1925, The Possible Relationship between Acromegaly and Diabetes, Arch. Int. Med. **37** 489 (April) 1926

5 Ellis, A. W. M. Hyperglycemia and Glycosuria in Acromegaly with Pathological Report by Prof. H. M. Turnbull, Lancet **1** 1200, 1924

6 Arnold, J. Weitere Beiträge zur Akromegaliefrage, Virchows Arch. f. path. Anat. **135**:1, 1894

7 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66** 332, 1908

100 personally observed patients. Whatever percentage may be agreed on, it is universally conceded that the association of true diabetes with acromegaly is strikingly frequent and "greater than with any other known disorder."

At this point it may be desirable to contrast the specific and outspoken pathologic condition characteristic of acromegaly, invariably found in the anterior lobe of the hypophysis, namely, a chromophilic adenoma, with the inconstant, meager, and relatively unconvincing changes in the Langerhans tissue of the pancreas, supposedly the seat of diabetes mellitus. From the standpoint of microscopic changes, the origin of acromegaly is constant and settled, whereas the unitary pathogenesis of diabetes mellitus is seriously open to question.^{7a}

We may now address ourselves to the hypotheses advanced for the disturbances in carbohydrate metabolism so frequently accompanying acromegaly. They have been conveniently divided under two captions (*a*) the neurogenic and (*b*) the endocrine.

THE NEUROGENIC HYPOTHESIS

The first explanation was advocated many years ago and still has strong adherents. Thus Colwell,³ in a recent article, gave as his opinion that the hypophysis is probably without significance in the field of carbohydrate metabolism as a gland of internal secretion. He favored the point of view that important nerve centers or pathways situated near the hypophysis in the hypothalamus are concerned with the control of secretion of insulin. In this connection Cushing and Davidoff² pointed out

Of the two forms of diabetes, diabetes insipidus, though the rarer, is far more entitled to be considered as a hypophyseal or parhypophyseal symptom than is diabetes mellitus. But when one considers that diabetes insipidus is practically unknown as a complication of pituitary adenomas, whether acromegalic or hypopituitary, no matter how large they grow to be or how much they may chance to deform the infundibulum and third ventricle, we may well pause before ascribing diabetes mellitus to the pressure of a pituitary adenoma against some still more hypothetical nerve center in the neighborhood. And of this we may speak the more emphatically since the far more numerous chromophobe adenomas of comparable size are rarely accompanied by glycosuria.

In short, the size of tumor and the pressure against the brain as a cause of the diabetes can be entirely discounted. The essence of the matter lies in the fact that only one particular variety of adenoma, irrespective of its size, is prone to cause the disturbance of sugar metabolism which may go on to the production of diabetes mellitus. This particular kind of adenoma is that composed of chromophilic cells which accompanies acromegaly.

7a "The accepted theory of diabetes as a disorder of the islands of Langerhans has found meager substantiation from the anatomic standpoint" (Yater, W. M. Acromegaly and Diabetes, Report of Six Cases, *Arch Int Med* **41** 883 [June] 1928)

This brief statement suffices for the purposes of this paper. The reader may pursue this discussion further in the articles already referred to.

THE ENDOCRINE HYPOTHESIS

It seems unnecessary to implicate the thyroid and the suprarenal medulla in responsibility for acromegalic diabetes mellitus. That both these glands might influence carbohydrate metabolism is recognized, but it appears far fetched and devious to enmesh them in an explanation of hypophyseal diabetes.

The prevalence of hyperglycemia and glycosuria in acromegaly has been referred to, and it is also well known that the reverse states of high sugar tolerance and even hypoglycemia occur commonly in hypopituitarism. The latter phenomena not only have received clinical recognition, but have been confirmed by experimental hypophysectomies.

The endocrine relationship of acromegaly and diabetes mellitus may be considered from three points of view: (1) That acromegaly and diabetes are two separate and distinct clinical conditions, that their occurrence in the same patient is purely coincidental, and that the disturbance in carbohydrate metabolism is primarily and solely due to a lesion or functional impairment of the internally secreting portion of the pancreas, (2) that the hypophysis is primarily and solely responsible for the hyperglycemia, without participation by the pancreas, (3) that the hypophysis plays the leading rôle, but produces alterations in dextrose metabolism by the antagonistic effect of its hormones on secretion of insulin or insulin activity.

The first assumption may be summarily dismissed. It would be a preposterous strain on statistics and the laws of chance to claim an independent and coincident diabetes in from 25 to 40 per cent of acromegalic persons.

The second assumption, which, *per contra*, would make the hypophysis the sole agent for the hyperglycemia of acromegaly, is an interesting possibility, but remains unproved. No one as yet has succeeded in producing permanent diabetes mellitus by the experimental injections (over long periods) of pituitary extracts.

Potent preparations from the posterior (and intermediate) lobe have been available for many years and have been impressively effective in reducing the thirst and polyuria in diabetes insipidus, in hastening labor by contracting the uterus, and in other clinical states in which a powerful smooth muscle stimulant was indicated. But injections of posterior lobe extract into the experimental animal have failed to produce more than a transient glycosuria and hyperglycemia. Nevertheless, this hormone has its place in the clinical treatment of persons with diabetes because of its antagonistic action to insulin, and this discovery

by Burn⁸ has been beneficially utilized in counteracting the hypoglycemic reaction consequent to overdosage with insulin. A hormone which possesses this important characteristic can hardly be considered negligible in the field of carbohydrate metabolism.^{8a}

Acromegaly, however, is predominantly and, perhaps, exclusively a disease of the anterior lobe. It arises from a postadolescent hyperactivity of the acidophilic cells. It would seem logical, therefore, to ascribe the accompanying hyperglycemia and glycosuria to this excessive secretion from the anterior lobe. Unfortunately for the purposes of this argument, experimental evidence recording the effects on blood sugar of repeated injections of an active anterior lobe extract has not been published. That a potent extract exists has been demonstrated by Evans⁹ in his production of gigantic rats, but whether these animals with hyperpituitarism showed hyperglycemia and glycosuria was not disclosed. Such a report would be trenchantly significant, since gigantism is a preadolescent expression of hyperactivity of the anterior lobe in many respects comparable to the postadolescent manifestations that result in acromegaly.

In this connection, Cushing and Davidoff have pertinently called attention to the not infrequent glycosuria in pregnancy "during which, as first demonstrated by Erdheim and Stumme¹⁰ the hypophysial pars anterior enlarges and takes on additional activity." Another clinical observation of interest is "the recognized peak of diabetes in childhood at about 14 years" which led them to question "whether this is in any way related to a period of unusual activity of the anterior hypophysis."

8 Burn, J. H. The Modification of the Action of Insulin by Pituitary Extract and other Substances, *J. Physiol.* **57** 318, 1923.

8a Since this paper was written two articles have appeared which deal with this subject. Ulrich, H. The Antagonism Between Insulin and Pituitary Extract, Its Demonstration in a Patient with Acromegaly, *Arch. Int. Med.* **41** 875 (June) 1928. Yater, W. M. Acromegaly and Diabetes, Report of Six Cases, *Arch. Int. Med.* **41** 883 (June) 1928. Ulrich stated that loss of carbohydrate tolerance in hyperpituitary disease was due to an antagonistic inhibitory action, exercised by excessive pituitary secretion, probably of the posterior lobe, on normal insulin function. He reported a case of hyperpituitary disease with acromegaly and glycosuria in which this antagonistic action was demonstrated, and in which the effectiveness of insulin was much impaired. Ulrich expressed the opinion that this antagonism may vary in different patients and that insulin may therefore show varying degrees of efficiency in the treatment for hyperpituitary loss of carbohydrate tolerance. Yater found that the diabetes in six persons with acromegaly was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy.

9 Evans, H. M. The Function of the Anterior Hypophysis, Harvey Lecture Series, Philadelphia, 1923-1924.

10 Erdheim, J., and Stumme, E. Ueber die Schwangerschaftsveränderung der Hypophyse, *Beitr. z. path. Anat. u. z. allg. Pathol.* **46** 1, 1909.

Considered singly these bits of evidence are inconclusive and circumstantial at best but marshaled together they become intriguing and persuasive. After all diabetes mellitus is only a clinical syndrome, not a specific disease, and there is justification for the suspicion that a lesion or even a functional weakness of the pancreatic islets is not an invariable or indispensable factor.

It must be admitted that in the present state of knowledge the third assumption seems the most conservative and the one that best fits the facts. Restated this hypothesis implies that the hyperglycemia and glycosuria of acromegaly are 'primarily hypophyseal, even though the pancreatic islets doubtless play a secondary rôle in their production'.

Putting aside the theoretical aspects of this question, which though fascinating are plainly debatable we may inquire into the effects on carbohydrate metabolism achieved by a direct attack on the acromegalic process itself. Some significant data exist on this point namely, the effect of hypophyseal operations on sugar tolerance in persons with acromegaly.

In 1924 Ellis⁵ recorded the interesting case of a woman, aged 42 who was known to have had acromegaly for ten years. She had shown diabetic symptoms for about eight months with a blood sugar level of 0.43 per cent and with 10 per cent glycosuria and large quantities of acetone bodies. She became sugar free after three days of fasting, and a limited diet for the following three weeks maintained this condition. The pituitary growth was then partially removed by a transfrontal operation. A trace of glycosuria was found postoperatively, but for the following three years despite an "increasing laxity of diet" she remained free from sugar in the urine although a hyperglycemia persisted. How much of this improvement following operation is real and how much is only apparent but actually due to elevation in renal threshold, cannot be answered. Cushing and Davidoff² reported the case of a woman, aged 22 who was first observed in December 1925 complaining of headaches. She showed osseous evidence of acromegaly but there was no disturbance of vision and the sella was small. At this time glycosuria was not present, but the blood sugar was 0.13 per cent. When the woman was seen again on Aug. 27, 1926, there was no glycosuria, but on Sept. 2, 1926 she was found to have a glycosuria amounting to 0.7 per cent. The blood sugar on September 10 was 0.14 per cent. Transsphenoidal decompression was performed, September 20 and the tissue removed showed an acidophilic adenoma. She made an excellent recovery with immediate cessation of her headaches and early subsidence of her "pituitary myxedema." Her blood at the termination of the operation on September 20 showed a sugar content of 0.24 per cent three days later, on September 24 it was 0.12 per cent on September 28 0.11 per cent and on October 1 0.09 per cent. In commenting on these

data the authors stated that this can hardly be considered a cure of a person with acromegalic diabetes, since the operation may merely have coincided with a wave of melituria, but that the postoperative fall in blood sugar was a significant phenomenon. They further report that in six patients, whose sugar tolerance was studied both before and after hypophysectomy, a definite postoperative lowering in the blood sugar levels was demonstrable. These observations are all the more significant since unusual pains were taken in the determination of the dextrose tolerance, the intravenous method being employed in preference to the ordinary oral procedure, thus insuring greater accuracy. Cushing and Davidoff made the following deductions from these observations:

(1) That the function of metabolizing carbohydrates is frequently impaired in acromegaly, amounting in many cases to actual clinical diabetes mellitus, and (2) that measures taken to reduce the hyperactivity of the pituitary anterior lobe seemed to have a beneficial effect on the patient's ability to handle sugars. Whether these findings indicate that the hypophysis may directly influence the capacity of the body to utilize carbohydrates, or whether the effect occurs only through some secondary disturbance of the glycolytic function of the pancreatic islets, there is as yet no positive way of determining. We are inclined to favor the latter view, but in either case the hypophysis so far as we can see plays the leading role.

As roentgen rays are known to depress cellular activity, and since this striking effect has been successfully utilized in diminishing the hyperthyroidism of exophthalmic goiter (not only clinically, but also in reducing the basal metabolic rate), since it has come into use as an adjuvant in controlling the size of pituitary tumors (Béclere,¹¹ Towne¹²), and since in one case at least its use amounted to a cure in a person with diabetes insipidus, it occurred to us that this therapeutic procedure might have some influence in diminishing hyperglycemia in a patient with acromegaly in whom normal vision and normal visual fields precluded the necessity for operative intervention. It is the encouraging outcome of this maneuver that forms the reason for this paper. The case in question is as follows:

REPORT OF CASE

M. M., a Spanish woman, aged 51, married, first came to the outpatient department, Feb. 23, 1926, complaining of headaches, rheumatism, dizzy spells, nocturia, insomnia, dyspnea on exertion and constipation.

She was married at 17 and had three healthy daughters. Her health had been good except for an appendectomy performed when she was 45 years old for an uncomplicated attack of acute appendicitis.

¹¹ Béclere, A. Technique, résultats, indications et contre-indications de la roentgentherapie des tumeurs hypophysaires, *Rev. neurol.* **38**: 808, 1922.

¹² Towne, E. B. Cessation of Diabetes Insipidus on Roentgen-Ray Treatment of Pituitary Gland, *J. A. M. A.* **83**: 2085 (Dec. 27) 1924, Roentgen-Ray Treatment of Pituitary Tumors, *Arch. Neurol. & Psychiat.* **15**: 92 (Jan.) 1926.

Catamenia began when she was 16, the flow was rather profuse, and lasted five or six days. Menopause followed the removal of fibroids, at the age of 45.

The present illness can be divided into two parts. Polydipsia, polyuria and polyphagia had been present for approximately twenty years. These symptoms had gradually increased in severity. Her height was 5 feet (153 cm), she had gradually become heavier after the age of 20, and her weight had increased from 194 to 204 pounds (88 to 92.5 Kg) in the past year. For at least twelve years prior to that she had weighed between 190 and 195 pounds (86.2 and 88.5 Kg).

At about 40 years of age there was a noticeable change in her appearance, and since then there had been a gradually progressive enlargement of the nose, lips, tongue, jaw, malar bones, superciliary ridges, calvarium, hands, feet, ribs and sternum. Accompanying this there had been a gradual loss of strength. Her shoes, gloves and hats now had to be considerably larger than formerly (figs 1 and 2). About eight years before admission, she began to have headaches which varied in intensity but which were constant in some degree through the day. She was quite nervous in crowds and occasionally somewhat irritable at home. There had been some forgetfulness during the previous year. She had had fre-



Fig 1—Appearance of patient at the age of 32 years, before development of acromegaly

quent drenching sweats above the waist during the past two years and perspired profusely when excited or working. Her hands and feet felt cold, and she had a cold sensation in the back of her neck. For the past ten years she had had pains in her ankles, knees, shoulders, sternoclavicular joints, costochondral region and finger joints. These joints had been swollen and red, and had shown hard, white nodules at times.

The woman was short, dark and obese, with typical acromegalic facies (fig 2). The skin was thick and rather dry. The hair was coarse and oily, and displayed masculine distribution with a few coarse hairs on the chin and about each nipple, masculine pubic escutcheon, and much hair on the thighs, upper legs and forearms. The head was large, with heavy supra-orbital ridges and zygomatic protuberances. The nose was large and bulbous. The face was broad, with mandibular prognathism. There was spacing of the upper incisors. The tongue was enlarged and thick and showed transverse furrows. The thyroid gland was of normal size, shape and consistency. The chest was barrel-shaped, and the manubrium sternum was prominent. The lungs were normal. The heart was slightly enlarged, and there was a blowing systolic murmur at the apex. Enlargement of the arch was not present. The peripheral vessels were

not palpably thickened. The systolic blood pressure was 125, diastolic, 80. The breasts were large, obese and pendulous. Great folds of skin and fat were present below the costal margin on each side, there was a heavy panniculus adiposus over the abdomen, and the hips and thighs were huge. The legs were less obese (fig 2). The feet and hands were broad, thick and spade-like (fig 3).

The Wassermann test of the blood was negative. The specimen of urine was clear, with a specific gravity of 1.009, and did not reveal any abnormalities in routine examination. The average daily fluid intake and output for three days on an unrestricted diet was 2,750 cc. The phthalein output was 50 per cent for

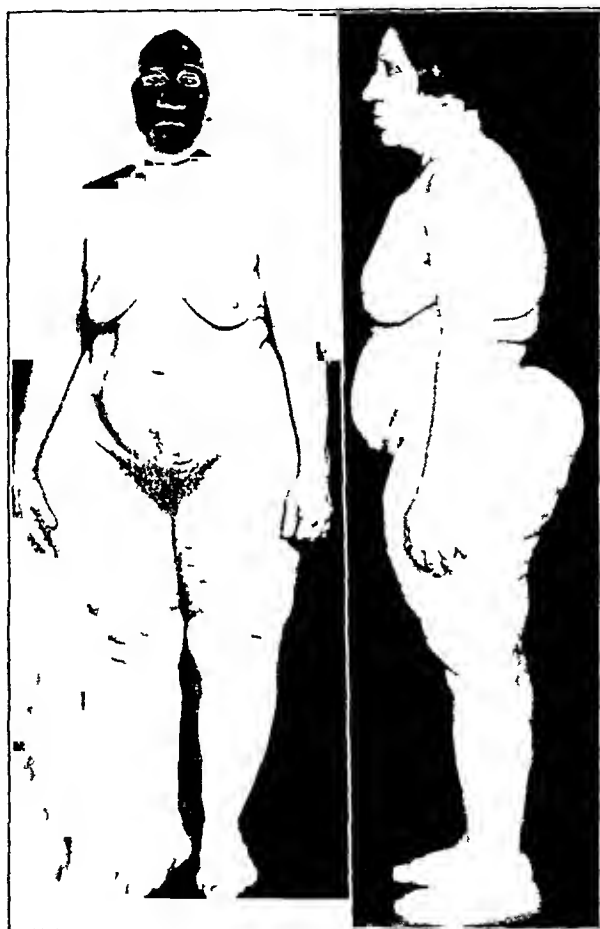


Fig 2—Front view and profile of acromegalic patient, aged 51 years, prior to dietetic therapy. The enlargement of the end of the nose, deep nasolabial folds, massive jaw, sternal protuberances, mild cervicodorsal kyphosis, broad feet, enormous girdle obesity and heterosexual pubic escutcheon should be noted.

two hours. The blood count and routine examination of the stools gave negative results. The basal metabolic rate was 127 per cent plus.

Roentgenograms of the skull showed the sella turcica to be oval and well roofed over by the anterior and posterior clinoid processes which closely approximated each other. The skull showed thickening of the calvarium, proliferation of the cranial air sinuses, and prognathism, characteristic of acromegaly.

Tests of the vestibular apparatus did not reveal any abnormalities.

Repeated examinations of the eyes on March 8, 1926, March 17, 1927, and July 14, 1927, did not show constriction of the visual fields and signs of increased intracranial pressure. The fundi showed the typical yellow disks of acromegaly, and the nasal half of each disk was somewhat hyperemic.

On May 25, 1926, the dextrose tolerance test (oral method, 100 Gm of dextrose being used) showed a fasting level of 0.119 per cent, a half hour after the administration of dextrose, 0.214 per cent, one hour after the administration of dextrose, 0.300 per cent, and two hours after the administration of dextrose, 0.234 per cent. Sugar did not appear in the urine at any time during the two hour test, indicating a high kidney threshold. It was determined at first to treat the patient as if she had an ordinary case of diabetes mellitus.

Under a quantitative dietary regimen, which kept the blood sugar within the normal zone and which reduced her weight from 93 Kg (204.6 pounds) to 65.5



Fig 3—Appearance of patient's acromegalic spade hand as compared with the hand of a normal control

Kg (144.1 pound) in nine months, there was general physical improvement (fig 4). Polydipsia, polyuria and polyphagia disappeared within three days after treatment was started. Headaches became mild and infrequent. She became happier and more active and energetic. A second dextrose tolerance test done at the end of this period (Feb 9, 1927) did not show definite improvement in the glycemia curve (fasting — 0.120 per cent, half hour after dextrose, 0.285 per cent, one hour after dextrose, 0.275 per cent and two hours after dextrose 0.227 per cent) but demonstrated definite improvement in the renal threshold, qualitative tests on the one hour and two hour specimens of urine showing traces of dextrose.

This lowering of renal threshold to a point near the normal level is frequently seen in the treatment of patients with ordinary forms of diabetes mellitus. The occurrence of such a reduction in this case would indicate that the pituitary gland does not have any influence on renal threshold, and therefore these patients

will show glycosuria when their blood sugar goes above their renal threshold, provided the urine is not too dilute to give a positive test with the ordinary reagents

In view of the lack of improvement in dextrose tolerance, despite adequate dietary control of the diabetes, further treatment was directed toward the acromegalic condition *per se*, by instituting two courses of roentgen-ray treatments to the hypophysis

One month after the first course of roentgen-ray therapy, another dextrose tolerance test was made and some improvement could be seen. This third test showed fasting — 0.118 per cent, a half hour after dextrose, 0.194 per cent, one hour after dextrose, 0.258 per cent, two hours after dextrose, 0.215 per cent. The maximum height of glycemia was 0.258 per cent as compared with 0.285 per cent, which was the lowest maximum of the two previous tests, and the two hour level was down to 0.215 per cent as compared with 0.227 per cent and 0.234 per cent in the tests prior to roentgen-ray treatment. The renal threshold showed further reduction, in that dextrose was present as a moderate trace in the half hour specimen, and in heavy traces in the one hour and two hour specimens.

The fourth dextrose tolerance test made on Sept 15, 1927, four months after the first course of roentgen-ray therapy, showed a height of only 0.236 per cent,

Dosage and Technic

Date		Skin Target Distance	Filter	Spark Gap	Milhamper Minutes
4/12/27	Left side	12 inches	¼ mm copper 1 mm aluminum	9 inches	150
4/15/27	Right side	12 inches	¼ mm copper 1 mm aluminum	9 inches	150
5/16/27	Right side	12 inches	¼ mm copper 1 mm aluminum	9 inches	75
5/24/27	Left side	12 inches	¼ mm copper 1 mm aluminum	9 inches	75
9/28/27	Right side	12 inches	¼ mm copper 1 mm aluminum	9 inches	120
10/ 3/27	Left side	12 inches	¼ mm copper 1 mm aluminum	9 inches	120
10/14/27	Right side	12 inches	¼ mm copper 1 mm aluminum	9 inches	120
10/21/27	Left side	12 inches	¼ mm copper 1 mm aluminum	9 inches	120

and the two hour level was within the normal zone, being 0.105 per cent (fasting, 0.124 per cent, a half hour after dextrose, 0.206 per cent, one hour after dextrose, 0.236 per cent, and two hours after dextrose, 0.105 per cent). There was no gross evidence of further improvement in renal threshold.

During the entire period of roentgen-ray therapy and in the four month's interval between the two courses of treatment, the diet remained the same as in the previous nine months of dietary treatment alone (protein, 70, fat, 120, carbohydrate, 60, calories, 1,600). The weight fluctuated between 144 and 149 pounds (65.3 and 67.6 Kg.)

A second course of four roentgen-ray treatments to the hypophysis was then instituted, and the fifth dextrose tolerance test, one month later, Nov 29, 1927, gave the following values. Fasting — 0.126 per cent, half hour, — 0.216 per cent, one hour, 0.183 per cent and two hours, 0.147 per cent. A comparison of these five curves has been charted in figure 5, and presents evidence of progressive improvement since roentgen-ray therapy was instituted.

In September, 1927, the patient was photographed again, and figure 4 shows the same osseous acromegalic characteristics, as was to be expected, but reveals the great loss of weight achieved by the dietary treatment.

In October, 1927, following the second course of roentgen-ray therapy, the patient volunteered the information that her headaches were still further reduced in frequency and severity. A roentgenogram (fig 6) of the skull taken at this

time showed some enlargement of the sella with thin floor, large sinuses and marked thickening in the frontal region. A roentgenogram of the hands (fig 7) showed short, heavy metacarpals, except the second, which was about normal. The phalanges were short and the terminal segments were characteristically tufted.

The eye fields were still normal as late as Nov 22, 1927. It might be stated that the perimetric studies were performed carefully by Dr Crawford, various sized test objects, and both artificial illumination and sunlight being used.

Apparently the roentgen-ray therapy did not have any effect in reducing the basal metabolic rate, which was 13.2 per cent plus on Nov 8, 1927^{12a}.

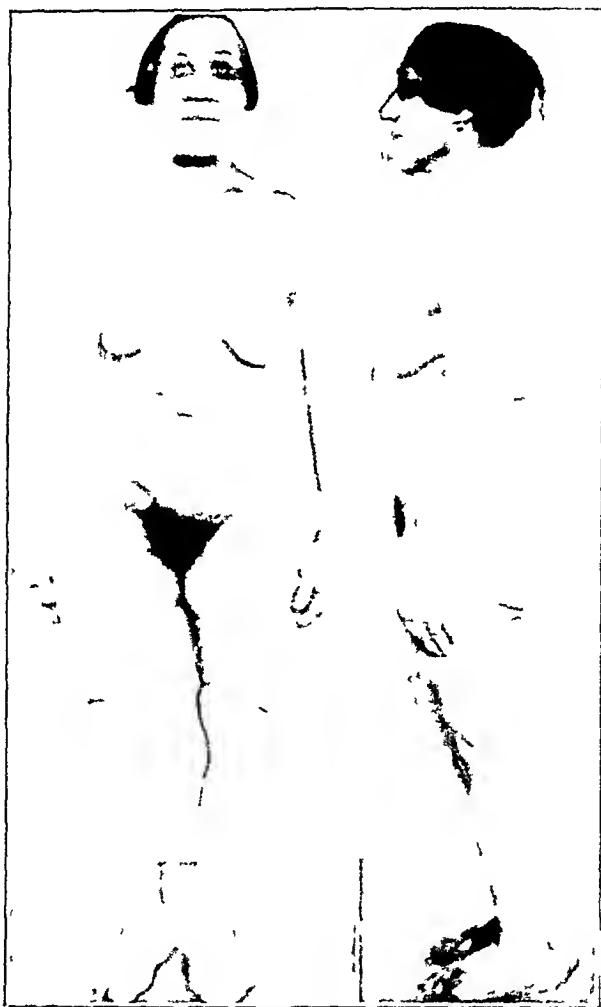


Fig 4—Front and profile views of patient following nine months of diabetic dietary regimen, resulting in a loss of 60 pounds (27.2 Kg). Compare with figure 2.

12a. A third basal metabolic rate was taken in June, 1928. It proved to be 3.5 per cent plus. A third course of roentgen-ray treatments to the hypophysis had been given in April, 1928. A sixth dextrose tolerance test was made June 19, 1928: fasting, 0.110 per cent, a half hour after dextrose, 0.205 per cent, one hour after dextrose, 0.222 per cent and two hours after dextrose, 0.155 per cent. The third course of inhibitory roentgen-ray therapy seemingly reduced the basal metabolic rate, but failed to effect any further increase in dextrose tolerance.

COMMENTS AND CONCLUSIONS

The experience detailed seems to warrant the following deductions

- 1 As noted by others, hyperglycemia without glycosuria may occur in acromegaly as in ordinary diabetes mellitus
- 2 The sugar tolerance in acromegaly may be unaffected by adequate dietary management
- 3 Roentgen-ray therapy to the hypophysis in acromegaly may favorably influence dextrose tolerance

We anticipate the following criticisms

- 1 The diabetes of acromegaly differs from ordinary diabetes mellitus by reason of its "fluctuating character", and whereas a complete cure of persons with true diabetes has never been accomplished (stoppage of

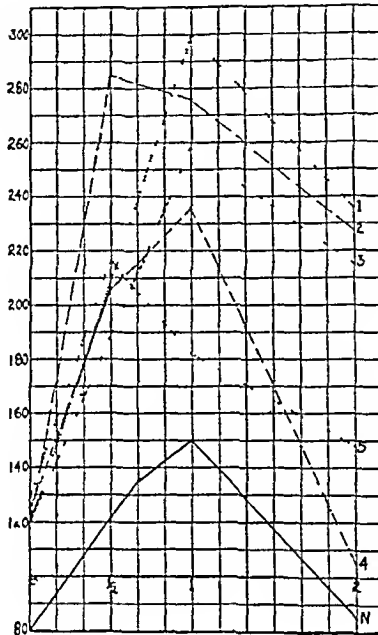


Fig 5—Composite chart depicting the five dextrose tolerance curves of the acromegalic patient, together with a normal curve for comparison (The latter is marked *N*) The sequence of the curves is indicated by the numerals on the right side The initial point of each curve represents the fasting level, the second point is the level one-half hour, the third point one hour, and the end point two hours, respectively, after dextrose was given For further details see test in text The striking feature of this chart is the progressive lowering of the blood sugar levels consequent to roentgen-ray radiation of the hypophysis

insulin and unrestricted diet without hyperglycemia), spontaneous cure of acromegalic diabetes has occasionally been observed ^{12b} The beneficial effect of the roentgen-ray therapy in our patient may be contested for

12b Yater (cited before) concluded that "the only difference between diabetes alone and diabetes associated with acromegaly is its occasional spontaneous temporary or permanent disappearance, a point which has been demonstrated in relatively few cases"

this reason, and it may be argued that the lowering of the blood sugar curve merely coincided with a spontaneous remission of her acromegaly. In this connection, we desire to call attention to the following points: (a) During nine months of dietary therapy, the blood sugar remained constantly between 0.10 and 0.12 per cent, but dextrose tolerance was uninfluenced until roentgen-ray therapy was instituted, (b) during the subsequent nine months' period of unchanged diet plus roentgen-ray therapy, a progressive improvement of dextrose tolerance was noted,



Fig 6—Lateral roentgenogram of the skull of patient shown in figures 2 and 4. The enlargement of the sella with thin floor, large sinuses, thickening of the calvarium, especially in the frontal region, and prognathism should be noted

as is depicted in figure 5, and (c) there was no other clinical evidence of diminished activity of the anterior lobe, and the basal metabolic rate was still slightly above normal. This mild elevation of the basal metabolism in acromegalic patients has been recently emphasized by Cushing and Davidoff,¹³ as has also the reverse state of an abnormally low

13 Cushing, H., and Davidoff, L. M. Studies in Acromegaly. IV. The Basal Metabolism, *Arch Int Med* 39: 673 (May) 1927.

basal metabolic rate in verified cases of hypopituitarism. If a lowering of the basal rate by either hypophysectomy or inhibitory roentgen-ray therapy is a gage of activity of the anterior lobe in acromegaly, then our case would seem to have been uninfluenced, but at least this would seem to answer the objection that the sugar tolerance was raised by a spontaneous reduction of the acromegalism.

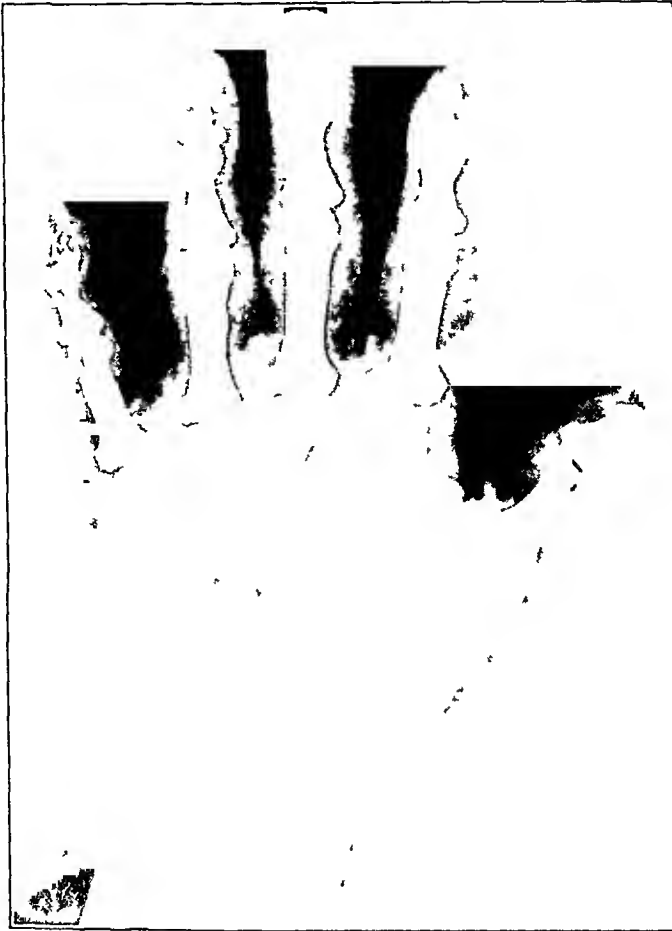


Fig 7—Roentgenographic appearance of the patient's hand. The short, heavy metacarpals, short phalanges and characteristic terminal tufting should be noted.

2 The second criticism might be that it is false reasoning to ascribe the improvement in dextrose tolerance to the irradiation of the hypophysis, since such improvement may gradually occur during a long dietary regimen, and that our patient was continually on a restricted diet. To this we would rejoin that this improvement did not appear during nine months of dietary management, which is unusual in ordinary diabetes mellitus, and that this improvement promptly followed the roentgenization of the hypophysis.

3 The third objection that might be raised concerns the use of the alimentary method for the determination of dextrose tolerance, as a criterion of improvement. Although we admit that the intravenous administration of dextrose is a more accurate procedure for research purposes, we are inclined to believe that the variability in the degree of absorption of sugars given by the oral method is of minor character, and would not account for the progressive decline in blood sugar levels noted in the case reported. Furthermore, it must be conceded that the oral method is the customary one employed by most authorities on diabetes.

This has been our first experience and, so far as we are aware, the first to be published, of the effect of roentgen-ray therapy of the hypophysis on dextrose tolerance. The results have been sufficiently encouraging to warrant its further use in this patient, in the hope of finally attaining a normal or subnormal blood sugar curve. When this has been accomplished, it will be interesting to watch developments when the patient is released from a low dextrose intake. If the curve remains normal under such conditions, we may feel justified in assuming that the patient's abnormal response to dextrose was directly, or at least primarily, due to the exaggerated secretion from the pituitary pars anterior.

SYPHILIS OF THE STOMACH

WITH SPECIAL REFERENCE TO CERTAIN DIAGNOSTIC CRITERIA*

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Some time ago (1925), one of us (F D) resected the distal one third of a stomach which was thought to be the seat of a carcinoma. From the gross and microscopic appearances of the specimen, together with the clinical history, we considered the changes to be syphilitic. In the sections examined, we failed, however, to demonstrate the presence of either *Spirochaeta pallida* or the classic gumma (the term "classic gumma" will be defined later). Two experienced pathologists who were consulted at the time did not consider sufficient evidence of syphilis to be present to justify an anatomic diagnosis of syphilitic gastritis. We entertained no doubt as to the correctness of their opinion and discarded our original conclusions without hesitation.

More recently one of us (H A S) has had the opportunity of studying three similar specimens. Two were resected by Dr K A Meyer at the Cook County Hospital and the third by Dr C A Hedblom at the Research and Educational Hospitals of the University of Illinois. In all three cases, the clinical and laboratory data and the associated lesions (hepatic gummas), found at postmortem observation of one, pointed to syphilis as the etiologic factor of the gastric lesions. Attempts to discover *Spirochaeta pallida* or classic lesions in the tissues sectioned were uniformly unsuccessful. The same pathologists were again consulted, with the same outcome, namely, that in their opinion there was insufficient evidence on which to base the diagnosis of syphilis of the stomach.

We desired to know how many of the cases reported and generally accepted as syphilitic gastritis were actually proved according to the criteria prescribed by the two pathologists mentioned. In order to gratify this desire, it became necessary for us to undertake an independent inquiry, the results of which are recorded. We considered as proof of the existence of syphilis of the stomach the demonstration of either the spirochete of syphilis or the classic gumma.

The entire literature on acquired syphilis of the stomach contains only one case in which the bacteriologic observations in the tissues led to

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its acceptance as a proved instance of syphilitic gastritis. In 1922, McNee¹ reported the presence of unusual lesions which he regarded as syphilitic, in a stomach removed at postmortem. From the involved area, eight blocks of tissue were excised and stained according to the Levaditi method. McNee's description reads:

In sections from one block only, spirochaetes were discovered in great numbers penetrating deeply in the actively growing granulomatous tissue. Near the free surface the spirochaetes in the necrotic layer were mixed with other organisms, but in the deeper granulation tissue close to the muscular coat they were unaccompanied by any other demonstrable organism. They had the typical appearances of *Treponema pallidum*, having from eight to fourteen small and regular curves.

McNee's case is generally quoted as the only one of acquired syphilis of the stomach in which *Spirochaeta pallida* has been demonstrated. So far as we have been able to ascertain, no one has challenged McNee's opinion as to the type species of *Spiillum* in his sections. It seemed rather odd to us that of all the attempts to demonstrate *Spirochaeta pallida* in cases of acquired syphilitic gastritis, McNee's alone should be crowned with success. This circumstance in itself, however, did not raise any question in our minds as to the correctness of his observation. What led us to doubt the diagnosis as to the type of *Spiillum* present was the fact that the organisms were so plentiful. Any worker who has at one time or another engaged in the search for spirochetes in acquired tertiary lesions of syphilis is well aware of the paucity of organisms and the patient search which is required to find even two or three. In one microscopic field of McNee's Levaditi preparation, at least eighteen distinct spirochetes are represented. Such pictures are not infrequently encountered in congenital syphilis, but rarely if ever in acquired tertiary lesions.

In order to differentiate between certain types of spirochetes, the use of the dark field is practically essential. When the examination is limited to the appearance of the organisms in tissues, little weight can be placed on the distinguishing features. The pictures of the spirochetes by McNee are similar, if not identical, with those of Vincent as found for instance in tissue which is the seat of a saprophytic infection. The resemblance is readily recognized when comparison is made between the organisms in McNee's illustration and those demonstrated by Pilot and Davis² in sections of tissue of the lungs taken from

1 McNee, J. W. Syphilis of the Stomach, *Quart. J. Med.* **15** 215, 1921-1922.

2 Pilot, I., and Davis, D. J. Studies in Fusiform Bacilli and Spirochetes, *Arch. Int. Med.* **34** 313 (Sept.) 1924. (Especially figures 4 and 11.) Pilot, I., Davis, D. J., and Shapiro, I. J. Studies on Fusiform Bacilli and Spirochetes, *Am. Rev. Tuberc.* **8** 249 (Nov.) 1923 (fig. 4).

patients with pulmonary abscess and gangrene. In their work on pulmonary fusospirochetosis, Pilot and Davis confirmed the observation of others that there occurs beyond the area where fusiform bacilli are found in association with spirochetes an advance zone in which spirochetes alone are present. These observations appear to be identical with those described by McNee, for, according to his report, "the spirochetes in the necrotic surface layer were mixed with other organisms."

The frequency of spirochetes in ulcerating lesions of the stomach is too well known to require emphasis here. Based on his study of the presence of spirochetes in carcinoma, Simmonds³ concluded that these organisms demanded attention because of the possibility of confounding them with *Spirochaeta pallida*. Fraenkel,⁴ in discussing Simmonds' paper, pointed out that from the photomicrographs which portrayed the spirochetes alone, a differentiation could not be made between the spirochetes found in carcinoma and the causative organisms of syphilis. This view is substantiated by the careful bacteriologic studies of Arnheim.⁵

In the case report to follow, a number of spirochetes were found in Levaditi preparations made from the ulcerated areas. These organisms were present on the whole in association with fusiform bacilli and other bacteria. Occasionally, however, spirochetes were found beyond the zone of bacterial invasion. We classified these spirillums as *Spirochaete vincenti* and are inclined to place the organisms found by McNee in the same category. We accept McNee's case as one of gastric syphilis, not on the basis of the bacteriologic observations, but because we consider the anatomic changes sufficiently characteristic to warrant this diagnosis. As a result of the investigation carried out in connection with our cases and those published in the literature, we were led to conclude that the causative organism of syphilis has not been demonstrated in any instance of gastric syphilis reported.

Before entering on a discussion of syphilitic lesions in the stomach, we desire to direct attention to current conceptions of the pathologic anatomy of syphilis in general. An authoritative and clear exposition of the subject is furnished by MacCallum,⁶ who, in discussing the pathologic condition of the tertiary stage, stated

The most characteristic, though not the most common manifestation of the affects of the spirochaetae in this stage of the disease is the gumma, which receives its name from its elastic, rubber-like consistency (Gummigeschwulst)

3 Simmonds. Ueber Spirochatenbefunde in Karzinomen, München med Wchnschr 55 1103, 1908

4 Fraenkel, E. Discussion on Simmonds (footnote 3)

5 Arnheim, G. Die Spirochaten bei Lungengran und ulzerierendem Carcinom (Kulturversuche), Centralbl f Bakteriöl 59 20, 1911

6 MacCallum, W. G. A Text Book of Pathology, ed 3, Philadelphia, W. B. Saunders Company, 1924, p 708

Most commonly such nodules are found embedded in the tissue and surrounded on all sides by radiating fibrous tissue which in itself is not especially peculiar. But the central portion is firm, elastic, opaque and yellowish-white like hard cheese. This is the necrotic caseous part, analogous to that found in tubercles but different in its elastic, firm consistency and in the slighter tendency to liquefy. In it one may sometimes discern faint outlines of pre-existent tissue now necrotic. Such nodules may be of almost any size from middle points to large masses. In the miliary gummata there may be no caseation or coagulative necrosis and the nodule is seen as a more or less concentrically arranged group of epithelioid cells richly mingled with mononuclear wandering cells and occasionally with giant cells. The arrangement is usually indefinite and irregular, lacking the sharpness and precision of the architecture of the miliary tubercle.

The impression is gained from the foregoing quotation and from other textbook descriptions that the term *gumma* may be correctly applied to practically any circumscribed chronic granulomatous lesion occurring in syphilis irrespective of size or the presence or absence of caseation. However, there is a definite tendency on the part of pathologists to choose as the most distinctive lesion of syphilis that type of *gumma* pictured by MacCallum in a testis (p. 706) and referred to by Kaufmann⁷ as fully developed. In this mature lesion, both the gross and microscopic features are unique. In histologic sections as stated by Kaufmann, one can distinguish three zones, namely (1) a caseous center the result of coagulative necrosis, (2) a middle zone of fibrous tissue with a limited number of recently proliferated and infiltrated cells and (3) an outer layer of younger granulation tissue rich in inflammatory elements. Macroscopically, when of sufficient size, the fully developed *gumma* yields a rubber-like consistency, and therefore represents a true "*gummigeschwulst*" seen especially in the liver, brain and testis. It is this particular type of *gumma* which, when present, is of the greatest value in identifying the infection as syphilitic and in separating the syphilitic from other types of granuloma. As the lesion described may be considered the most characteristic of tertiary syphilis, it is referred to as the "*classic gumma*."

A painstaking search through the literature on gastric syphilis failed to disclose within the stomach a single instance of a *gumma* answering to the gross and microscopic description of the fully developed one. Even the certain or almost certain cases of gastric syphilis gathered by Konjetzny⁸ in his comprehensive treatise on the subject lack cases showing classic *gummas*. Analysis of the original reports referred to by

⁷ Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie*, ed 7 and 8, Berlin, 1922, vol. 8, p. 1586.

⁸ Konjetzny, G. E., Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, 1928, vol. 4, pt. 2, p. 1026.

Konjetzny (Klebs,⁹ Cornil and Ranvier,¹⁰ Birch-Hirschfeld,¹¹ Fraenkel,¹² Buday,¹³ Stolper,¹⁴ Brams,¹⁵ McNee¹) indicates that the gummas mentioned by those authors were almost invariably found to be circumscribed foci of granulation tissue densely infiltrated by inflammatory cells, but devoid of central necrosis en masse (in Brams' article the microscopic changes of his case are splendidly described and profusely illustrated)

Although classic gummas were absent in the stomachs, they were encountered in other organs, such as the liver, in more than a majority of the cases mentioned. If the gastric lesions recorded were actually syphilitic in origin, then the lack of classic gummas in those stomachs is to be explained on the basis of differences in the local response to the spirochetal invasion of this organ as compared with other organs.

A number of authors believe that the diagnosis of syphilis cannot be positively made on the basis of a single lesion, since, in their opinion, identical morphologic changes may result from another type of infection, for instance, tuberculosis. Pathologists in general choose to speak of the gumma as the characteristic rather than the specific lesion of syphilis, inferring thereby that this particular type of granulomatous tumor occurs most frequently but not invariably in syphilitic lesions. If, however, any single lesion is to be considered specific of the tertiary stage of syphilis, the classic gumma is entitled to first claim. In the following paragraphs the term specific lesion of syphilis refers to the classic gumma with the tacit understanding that specificity is assumed rather than proved.

As *Spirochaeta pallida* and the classic gumma, which represent respectively the specific organism and the lesion, constitute the only proofs of syphilis, we are forced to conclude that as far as we were able to ascertain, the medical literature does not contain a report of a true case of syphilis of the stomach. This conclusion, however, should not be

9 Klebs, E. Handbuch der pathologischen Anatomie, Berlin, 1869, vol 1, pt 1, p 260

10 Cornil, V, and Ranvier, L. Manuel d'histologie pathologique, ed 3, Paris, 1912, vol 4, p 482

11 Birch-Hirschfeld, F. V. Lehrbuch der pathologischen Anatomie, ed 4, Leipzig, 1895, vol 4, p 642

12 Fraenkel, E. Zur Lehre von der erworbenen Magen-Darm-Syphilis, Virchows Arch f path Anat **155** 507, 1899

13 Buday, K. Ueber einen ungewöhnlichen Fall von Syphilis, Virchows Arch f path Anat **141** 514, 1895

14 Stolper, P. Beiträge zur Syphilis visceralis (Magen-Lungen-Herz-syphilis), Bibliotheca medica, Cassel, 1896, no 6, pt C

15 Brams, W. A. Ueber das Ulcus syphiliticum multiforme ventriculi, Arch f Verdauungskr **27** 375, 1921

constituted to mean that the diagnosis of syphilis of the stomach in all cases reported as such is erroneous. As a matter of fact, evidence of gastric syphilis is so convincing in many of the reported cases that for clinical purposes they may be readily accepted as such even in the absence of actual proof.

We do not see any valid reason why the demonstration of the specific organisms in suspected cases of gastric syphilis should be demanded when it is generally conceded that *Spinochaeta pallida* is found in the lesions of acquired tertiary syphilis only exceptionally (Aschoff¹⁶). Nor do we see the logic of refusing to recognize as syphilis of the stomach a case in which classic gummas are lacking, since it is well known that the gummy tumor with central necrosis en masse is far less common than the less typical lesions of syphilis, and that, furthermore, in not a few locations the classic gumma is rarely seen (aorta, periosteum).

Throughout the body, granulomatous lesions are diagnosed as syphilitic on the basis of collective evidence even in the absence of specific indications. As experienced a pathologist as Fraenkel¹⁷ recommended in cases of questionable syphilitic aortitis the performance of the Wassermann test postmortem, as an aid in final diagnosis. MacCallum⁶ writes

The history of the case, the Wassermann reaction, the bacterial findings, the distribution of the lesions and their relationship to lesions elsewhere, their size, consistency, and gross appearance, their tendency to heal or to break down, and least of all their histological structure—these are the things upon which the diagnosis of syphilis in the tertiary stage may be based.

We are of the opinion that the standards which are customarily used in the diagnosis of syphilis elsewhere should be applied also to syphilis of the stomach, and that the critical pathologist should require simply a preponderance of evidence and not actual proof before accepting the case as one of gastric syphilis.

After reaching the foregoing conclusions regarding criteria for the diagnosis of syphilis of the stomach, we reviewed the facts in connection with our case of 1925. As a result of this later study, we felt that, in the light of our recently acquired knowledge and opinion, there was sufficient evidence to justify the diagnosis of syphilis of the stomach. We are presenting the case in some detail in order to give the reader an opportunity to judge for himself as to whether or not there are sufficient clinical, laboratory and pathologic data on which to base the diagnosis of syphilitic gastritis.

16 Aschoff, L. *Pathologische Anatomie*, ed. 6, Jena, 1923, vol. 1, p. 571.

17 Fraenkel, E., and Much, H. *Das Wassermansche Reaktion and der Leiche*, *München med. Wchnschr.* 55: 2479, 1908.

REPORT OF CASE

Clinical History—C D, a colored man, aged 38, was admitted to the medical service of the Cook County Hospital on Aug 21, 1924, with an examining room diagnosis of gastric syphilis. His presenting complaint was epigastric distress, which had begun eleven months prior to entrance. During the first nine months of the patient's illness, the distress although persistent had been relatively mild. At the beginning of the tenth month, the discomfort had been felt as an actual pain which had caused the patient to stay in bed, where he had remained for approximately four weeks. After his confinement, he had attempted to return to work, but had been compelled to remain home on account of the pain he experienced.

He had a burning pain accompanied at times by severe cramps. It was located in the epigastrium to the left of the mid-line and was circumscribed. The pain was felt on arising and was relieved for half an hour or so by breakfast. The same pain-food-ease sequence occurred in connection with the other meals. The relief from taking of food, however, was not constant. Pain at night had not been felt prior to entrance. The intake of soda was not followed by definite relief, but by vomiting which occurred usually after the noon meal had been eaten. Pressure applied to the epigastrium allayed the severity of the pain. Relationship was not noted between the pain and the quantity or quality of the food eaten.

The patient had lost 20 pounds (9 Kg) during that part of his illness previous to six weeks before hospitalization. During these six weeks, he had regained 10 pounds (4.5 Kg). Constipation had been marked throughout the eleven months, and the patient had required a cathartic in order to obtain a bowel movement. Other noteworthy complaints were not elicited in the routine inventory of symptoms by systems. He had contracted gonorrhea six times. In May, 1923 he had had multiple penile sores followed by bilateral bubo. He believed that the Wassermann reaction had been negative at that time. His occupation necessitated the handling of paint.

Examination—Physically he was well developed but somewhat undernourished. Abnormalities were not present, except for a slight generalized lymphadenopathy and multiple scars on the glans penis. The chemical analysis of the blood disclosed a moderate degree of secondary anemia. The diagnosis of chronic plumbism was regarded as the most likely, and the patient was placed on a treatment with phosphoric acid and potassium iodide, pending the results of further tests. The Wassermann reaction was reported 2 plus, on the basis of this report, mercury rubs and potassium iodide were prescribed. Sixty cubic centimeters of material with a free acidity of 12 and a total acidity of 35 degrees was aspirated one hour after the administration of an Ewald test meal. Occult blood was not detected in the gastric contents. Tests of two stools, one liquid and the other formed, were negative for chemical blood.

X-ray examination revealed. The stomach proper appeared normal during the screen study, but on the plate series lacked the perfect rounding of the pyloric end. A satisfactory duodenal bulb was not seen at any time. During the early part of the screen examination, a persistent pocket-like shadow was obtained at the right extremity of the base of the cap. There was a marked imperfection of the bulb which was fairly constant in the plate series. The diagnosis was duodenal deformity of sufficient degree to support a clinical determination of ulcer.

Course of Illness—The case was managed like cases of ulcer, and although the acidity was readily controlled, the pain persisted and was particularly noticeable during the night. After twenty-six days of trial, the Sippy ulcer regimen was discontinued, and nonspecific protein therapy was instituted. This afforded only temporary relief. The patient left the hospital on Oct 3, 1924, slightly improved.

Approximately three months later, he returned to the hospital, saying that the epigastric pain had increased progressively in severity. On physical examination, tenderness was elicited in the left epigastric region, where resistance was felt. An Ewald test meal yielded 240 cc of gastric contents, which showed 12 free and 23 combined degrees of acidity. Chemical blood was not found. The motor meal indicated retention after six hours, and the test for occult blood at this time was positive. Of six stools examined for blood, three showed a trace with the benidine test, the others proved negative. A smear of the bacteria in the stool showed a preponderance of the gram-negative flora. A second x-ray examination on Jan 12, 1925, disclosed a 4 ounce residue at the end of six hours and a pyloric defect which was interpreted as carcinomatous. The patient was transferred to the surgical service, with the diagnosis of carcinoma of the stomach. On January 19, exploration was undertaken by one of us (F D), and an indurated mass of unusual character occupying the pyloric area was palpated. Resection of the distal one third of the stomach was decided on and was carried out according to the Polya method. At the conclusion of the operation, as the patient was being moved from the table, he died suddenly. The mode of death resembled that which occurs in persons with latent syphilis of the brain who are subjected to general anesthesia (LeCount and Singer¹⁸). The coroner's physician, without making a postmortem examination of the body, attributed death to ether anesthetic.

Pathologic Report—The gross description read as follows. This specimen consisted of the resected pyloric portion of the stomach to which was attached the beginning duodenum. The specimen, which had the form of a thick, narrow tube, measured 11 and 65 cm along the greater and lesser curvatures, respectively. There was only a small amount of fat in the gastrocolic and gastrohepatic omentums. The lymph glands along the greater curvature were enlarged to the size of a bean, were firm in consistency and on section were a pale pink. The serosa covering the distal half of the specimen was white in places because of fibrous thickening. When opened along the greater curvature and viewed from the mucosal side, three irregular defects in the gastric lining were observed. The largest, which was located on the lesser curvature, extended to involve both anterior and posterior walls, and assumed a form somewhat suggestive of a cloverleaf. It measured 35 cm in its larger and 28 cm in its smaller diameter. The other ulcers located distally were approximately of equal size, and measured 24 and 22 cm in diameter, respectively. The largest of the three ulcers was scirrhous in outline, and, as compared with its extent, was quite shallow and superficial. The edges were not thickened or undermined, but were clearly demarcated from the surrounding mucosa and were adherent to the well outlined margins of the ulceration. The floor was smooth and covered with a grayish red membranous deposit which was easily removed. The two smaller ulcers were similar in all essentials.

18 LeCount, E R, and Singer, H A. The Hazard of Surgical Anesthesia with Syphilis of the Brain, *J A M A* 84 358 (Jan 31) 1925.

The mucous membrane between the ulcerations was for the most part unattached to the underlying submucosa, and was mammilated and devoid of rugous folds. The gastric wall was greatly thickened, beginning at a point 1.6 cm. distal to the proximal edge of the resected specimen and extending to the pyloric ring. The ulcers were located in the thickest portion of the specimen. On section, the thickening was seen to be due mainly to an increase of the submucosa which appeared white and succulent with whitish-yellow miliary and submiliary foci here and there. A number of sectioned blood vessels stood out prominently. The point of maximum thickness measured 1.8 cm., of which the submucosa comprised one half. The thickening gradually decreased in passing centrifrically from the zone of ulceration. The muscular layer was only slightly thickened, but was rendered somewhat prominent by contrast with the white submucosa. Distinct connective tissue septums were not seen to pass downward from the submucous to the subserous layer.

Microscopic Description—Blocks were removed from many regions, especially from those areas which appeared different grossly and which were prepared according to standard methods. In the description which is to follow the structural changes as determined by hematoxylin and eosin, van Gieson and Weigert elastic tissue and fibrin stains will be treated as they occurred layer by layer. The bacteriology and mycology for which Levaditi, Ziehl-Neelsen and Giemsa stains were utilized will be reported separately following the complete description of the pathologic-anatomic alterations.

Mucosa—At a distance from the margins of the ulcer, the mucosa appeared to be of average thickness and contained pits and tubules of normal appearance. In approaching an ulcer, the branched tubules gradually disappeared, leaving only crypts behind. Some of these were distended to form cystic swellings before the lining epithelium ended at the ulcer edge in a single horizontal layer of cells. The border of the mucosa was, as a rule, flush with that of an ulcer wall. The most noteworthy change in the mucosa was the presence of numerous lymphocytes, lymphoid and plasma cells, together with many macrophages and an occasional eosinophil, accumulated in the tunica propria. These cells were found in greatest numbers near the margins of the ulcer, but even at distant points they were present in abundance. For the most part, the infiltrate was a diffuse one, but here and there dense circumscribed collections resembling solitary nodules extended upward into the mucosa from the underlying layers.

Muscularis Mucosae—The muscularis mucosae was, in all the sections examined, greatly thickened, especially in approaching the ulcers. At the border of an ulceration, the muscular tissue became thin and divided, and was obscured entirely by a cellular mass which formed the wall of the ulcer. Along with the thickening of the muscularis mucosae, which was due mainly to an increase in connective tissue, there was a separation and division of its substance into strands and bundles. Between the divided elements were accumulations of lymphocytes, lymphoid and plasma cells and macrophages. Extensions from these foci appeared to pass into the mucous layer. Here and there a large, circumscribed collection of cells projected from the submucosa through the muscularis mucosae to involve the mucosa. The included fibers of muscle were in such areas represented by few remnants of the original tissue. The vascular changes here were similar to those to be described in connection with the next layer.

Submucosa—The submucosa was the seat of the most extensive and most marked changes. The thickening of the submucous layer, which under low magnification was its most conspicuous feature, was due to a diffuse production of granulation tissue associated with a chronic edema and the formation of dense inflammatory infiltrates. The involvement was present, not only in the immediate proximity of the ulcers, but also at a distance from them. The ulceration nowhere extended below the superficial portion of the submucosa. The floor of an ulcer was covered by fibrin, within the meshes of which were polymorphonuclear leukocytes and a cellular debris. Underlying the superficial fibrinous layer was a young granulation tissue rich in greatly dilated capillaries and cellular elements which consisted mainly of plasma cells. Beneath this layer of young granulation tissue were diffuse and circumscribed aggregates of cells in which the plasma variety overwhelmingly predominated.

The cellular infiltrates varied in size, circumscription and outline. In places the cells were thickly set, especially in the region of ulceration, in other places, they were rather widely separated by a loose, edematous granulation tissue. The well circumscribed accumulations of cytologic elements were for the most part round, and ranged from the size of a classic miliary tubercle to ten times that size. More or less diffuse, indefinitely demarcated, irregularly outlined collections of cells were found especially beneath the muscularis mucosae, penetrating into and separating its constituents into fractions and entering the mucosa. The intimate relationship of many of these aggregations to blood vessels was most conspicuous and will be discussed later. A striking feature was that the inflammatory infiltrates were, in almost all the sections examined, more prominent in the superficial one half of the submucosa. In the lower one half, the cellular elements tended to be perivascular in their distribution.

The cytologic elements comprising the submucosal aggregates were mainly lymphocytes, lymphoid and plasma cells in varying proportions, together with scattered macrophages and epithelioid cells. Some foci consisted entirely of closely packed lymphocytes, about which a few lymphoid and plasma cells were scattered. In others, the three types of cells were heterogeneously mixed and present in approximately equal numbers. At the base of an ulceration, the plasma cells greatly outnumbered the other types. Most of the cellular collections had a more or less uniform, dark appearance, and contained a few capillary blood vessels and a barely visible reticulum. A few, however, and these were generally located just beneath the muscularis mucosae, presented a light area, usually central, made up of a structureless material separating the granuloma cells, which were well preserved. Giant cells such as are found in the muscularis propria were not present in the submucosal foci.

The perivascular grouping of the granulomatous cells (figs 1, 2 and 3) was perhaps the most unique microscopic feature in the altered appearance of the submucosa. The infiltrated cells formed bands of varying thickness, partial or complete, about many of the vessels. The small and medium sized vascular elements were affected to a greater degree than the larger blood vessels. The perivascular infiltrates consisted of the same type of cells found in the aggregates, which were unrelated to the vessels. In addition to the perivascular structures, the blood vessels themselves presented evidence of active participation in the inflammation (figs 1, 2 and 3). A noteworthy fact was that the vascular involvement was peculiarly irregular in its distribution. One vessel may show extensive injury, a second a moderate degree of involvement and a third, located in an intermediate zone, may be entirely spared. This focal involvement was especially prominent in areas beyond the wall of the ulcer. The injury

to the vessels appeared to result mainly from granulomatous involvement similar to that found elsewhere. The invading elements were in some cases limited to the adventitia. In others, they extended to include the mediums and even the intima. Occasionally the intima, through multiplication of its lining cells, lead to narrowing or complete occlusion of a vessel lumen. In places, the combination of proliferation of the endothelial cells, granulomatous invasion and compression of the vessel was encountered (figs 1, *a* and 2, *a*). Although the picture of recent and active panvasculitis was frequently noted, the number of totally obstructed vessels was very small. In not all cases was the entire circumference affected, for here and there a nodular swelling which projected from a portion of the wall of the vessel could be seen. Changes



Fig 1—Vascular and perivascular involvement in the submucosa. One vein (*a*) is totally occluded due to endothelial proliferation, panvasculitis and compression. In the other two veins (*b* and *c*) the granulomatous cells are limited mainly to the adventitia. The walls of the arterial elements (*d* and *e*) although encompassed by dense cellular aggregates are invaded to only a slight degree. Magnification, 100 diameters.

of a chronic nature indicated by the presence of an increase of adult fibrous tissue in one or more layers was uncommon.

A noteworthy and remarkable feature was the focal distribution of the vascular injury. Often a series of sections might disclose the fact that simply a segment of a vessel was involved, and what was particularly striking was that in cross-section merely a sector of that segment might be affected. Another distinctive character was that the veins bore the brunt of the injury accorded the vessels, for involvement of the arteries was far less marked. In

fact, the severe degree of phlebitis often contrasted strikingly with the mildness of the arteritis. In many fields in which an artery was relatively uninvolved, the accompanying vein or veins were greatly damaged. The reverse, however, was not true. When obliteration of an artery was encountered, which occurred only occasionally, the caliber of the affected vessel was usually quite small. Occlusion of the venous radicals, however, was not limited to the finer elements. The larger vessels were relatively free from granulomatous involvement.

Study of the vascular changes was greatly aided by preparations stained for elastic elements. In many vessels, the elastic ring appeared to be intact and normal. In some instances, the lamina elastica was frayed but unbroken.

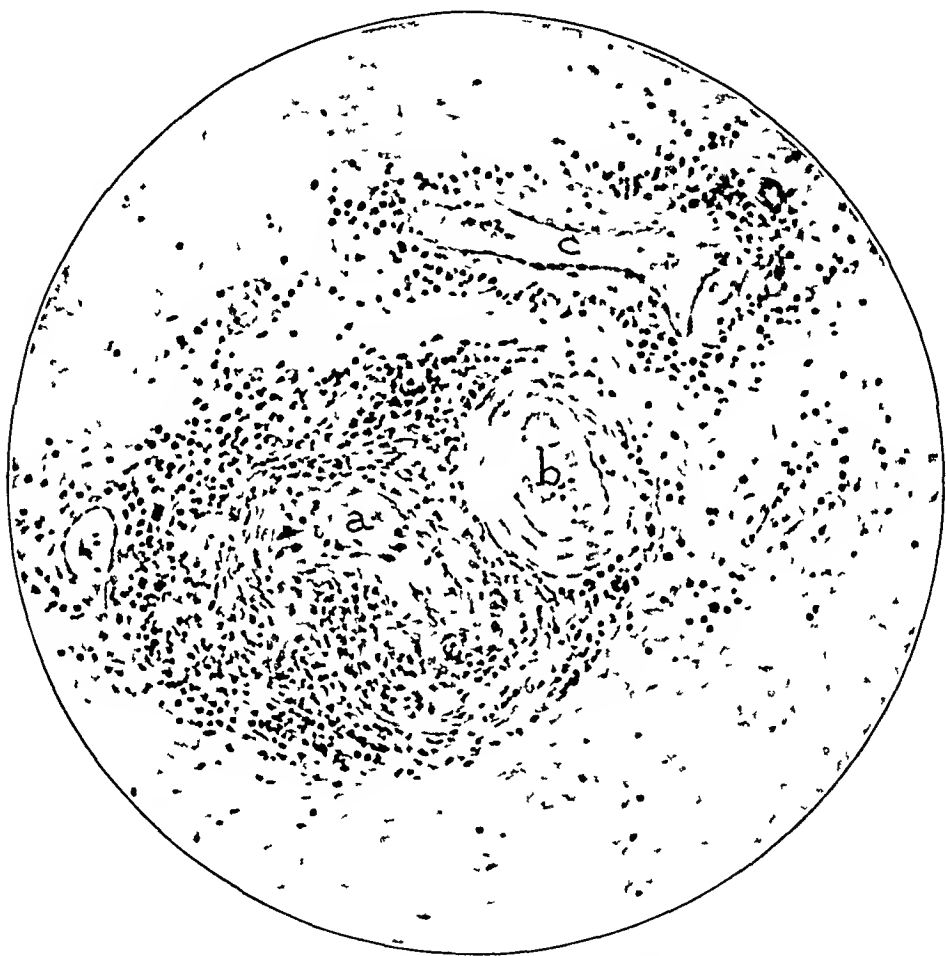


Fig 2—An area in the submucosa at a distance from figure 1. The endothelial proliferation and swelling, together with granulomatous invasion, obliterates one vein (*a*). The wall and lumen of the accompanying artery (*b*) are unaffected. In a neighboring vein (*c*) the granulomatous elements are seen to extend from the adventitia to the mediums. Magnification, 125 diameters.

Excessive separation of the elastic elements was associated, as a rule, with a marked alteration in the normal architecture of the involved vessel. In some instances, otherwise indifferent structures were identified as vessels solely by the presence of retained elastic rings. On the other hand, some of the diffusely involved vessels, principally veins, recognized as such with the aid of counterstains, had lost their elastic membranes entirely. Especially instructive were those pictures in which only a sector of a ring, corresponding to a localized granulomatous involvement of a vessel, had undergone elastolysis. The manner

in which vascular occlusion occurred was rendered clear in the sections stained by Weigert's method. The elastic membrane instead of practically bordering the lumen of a vessel was separated from the endothelial lining by constituents of the granuloma which encroached on the channel and produced a thickening of the wall of the vessel (fig 3).

The Muscularis Propria—This layer was also greatly altered, particularly in those areas in which the overlying submucosa showed high-grade changes. In that portion which was adjacent to the submucosa, there were found a slight thickening of the connective tissue and a marked increase of the elastic elements which normally occupied the boundary between the two coats. In the deeper



Fig 3—Endarteritis (a) and phlebitis (b) (Weigert's elastin stain, counterstained with lithium carmine). In each vessel the elastic membrane is separated from the lining endothelium by granulation tissue which encroaches on the vascular channel. The eccentric situation of the lumen of the artery is the result of excessive thickening of a portion of the circumference of the intima. Magnification, 150 diameters.

layers, although vascular involvement was not lacking, it was not nearly as prominent as in the submucosa. The perineural lymphatics and tissues were the seats of cellular accumulations which closely resembled the perivascular infiltrates already described. Extension of the inflammatory cells between the neural elements was not infrequently encountered.

The degree of involvement and the type of alteration found in the muscularis propria varied in different sections examined. In some of the areas

investigated, edema of the intermuscular septums was found associated with rather sparsely infiltrated lymphocytes and lymphoid and plasma cells, the last predominating. In other places there were, in addition, moderate numbers of cells gathered in spaces of tissue, forming linear collections between bundles of muscles. In still other areas besides the rather diffuse infiltrates, there were dense cellular accumulations constituting smaller or larger circumscribed foci which invaded and replaced the normal substance of muscle (fig 5). These foci were in the main round or oval, but here and there they were polymorphous. Some of the smaller foci were uniform, but the majority of these and practically all of the larger collections stained lighter in the central portions.

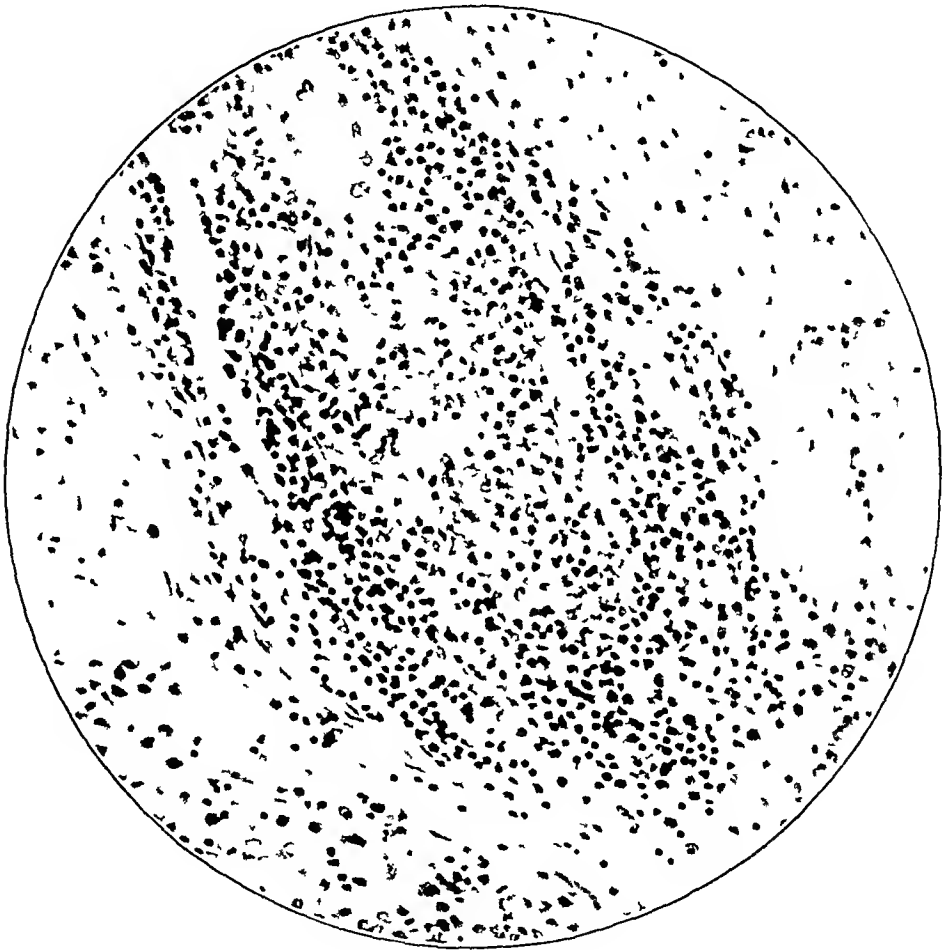


Fig 4—Miliary nodule located in a septum in the muscularis propria. Two multinucleated giant cells are present. Magnification, 225 diameters.

The circumscribed infiltrates which stained uniformly were composed of the same elements which constituted the submucosal aggregations. In the granulomatous foci with light centers (figs 4 and 5) corresponding to these pale-staining areas, threads and granular debris separating widely the individual cellular elements of the infiltrate were found. The granulomatous cells were well preserved, their nuclei stained distinctly and did not exhibit regressive changes. The structureless material between the cells appeared to be derived from the pre-existent tissue in which the granulomas had developed. Thus, smooth fibers of muscle could be traced from the periphery of a granuloma to its center where the fibers became transformed into granules. In some of

the giant cells, a few of these granules, in addition to nuclear remnants, were engulfed. The central portions of these granulomatous foci consisted of lymphocytes, lymphoid, plasma and epithelioid cells, together with mononuclear macrophages and Langhans giant cells supported by a delicate granulation tissue in which a moderate number of capillaries were found. The arrangement of the cells comprising the light-staining centers were strikingly indefinite and irregular and lacked the precision of architecture seen for instance in miliary tubercles. The peripheral portions of foci with pale-staining centers consisted mainly of closely packed round cells. Multinucleate giant cells were not present in the outer zones of the granulomatous nodules.

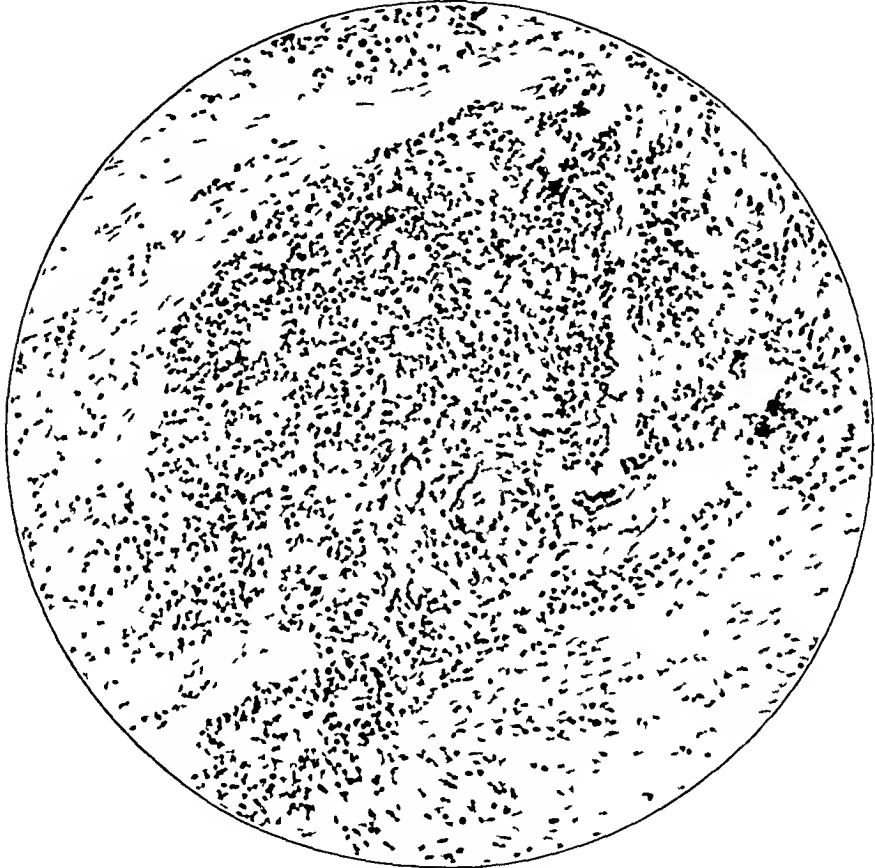


Fig 5—A miliary granuloma which has destroyed and replaced the original muscle fibers in the circular layer of the muscularis propria. In the region of the pale-staining granular debris there are four foreign-body giant cells. Magnification, 125 diameters.

Serosa—The peritoneal covering was greatly thickened, and its normal elements were widely separated, owing to an edema fluid and the presence of numerous round cells together with a few macrophages. The infiltrate, which was diffuse, was more marked in some parts than in others, but nowhere was there any tendency toward dense accumulation or circumscription of the inflammatory cells. The vascular and perivascular involvement was noted in this layer also, however, not to the degree seen in the other coats.

Bacteriology and Mycology—Specific stains for tubercle bacilli failed to disclose the presence of acid-fast organisms. In Levaditi preparations, in the

necrotic tissue forming the floor of an ulcer, were seen a number of spirochetes which had from four to eight coarse spirals resembling morphologically the spirilla of the mouth. These were found, on the whole, in association with fusiform bacilli and a number of other bacteria. Only occasionally could a spirochete invading intact tissue be identified beyond the fusospirochetal zone. Sections stained by the method of Giesma did not reveal any fungi.

SUMMARY AND COMMENT

At the time the case reported herewith came under observation (1925), we were led to believe that before the diagnosis of syphilis could be justifiably made the demonstration of either *Spirochaeta pallida* or the classic gumma was necessary. The experience of one of us (H. A. S.) with three subsequent cases in which the clinical, laboratory and anatomic observations pointed directly to syphilis of the stomach, but in none of which either of the foregoing requirements were fulfilled, led us to inquire into the frequency with which the spirochete of syphilis and the classic gumma were found in cases recorded in the literature as examples of gastric syphilis.

We were able to find but one report, that of McNee,¹ in which the demonstration of spirochetes in the gastric tissues led to its acceptance as one of proved acquired syphilis of the stomach. Critical analysis, however, proved to us that the organisms described and pictured were far more likely spirochetes of Vincent than *Spirochaeta pallida*. We therefore declined to accept McNee's diagnosis of the type of spirochetes present in his specimen, and concluded that in no case of acquired syphilis of the stomach has the spirochete of syphilis been satisfactorily demonstrated.

The most characteristic and, according to some authorities, specific lesion of syphilis is the fully developed (classic) gumma. It possesses an elastic (gummy) consistency apparently due to coagulative necrosis of a particular type. Other lesions found in syphilis, such as milium gummas and dense cellular infiltrates, exhibiting a perivascular arrangement, are not as distinctive. Although present in other organs, such as the liver, lungs and spleen, classic gummas were entirely lacking in the stomachs of all the cases of syphilitic gastritis available for analysis.

Since we were unable to discover in the literature on acquired gastric syphilis any instance in which *Spirochaeta pallida* or the classic gumma was actually demonstrated, we concluded that either the diagnosis of syphilis of the stomach was erroneous in all the cases reported or else our criteria were too stringent. In not a small number of cases, although actual proof in the form of the specific organism or lesion of syphilis in the stomach was lacking, the evidence for gastric syphilis was so preponderant as to force us to conclude that our previous standards were inappropriate. As a result of our study, we learned that the nature of

an acquired syphilitic infection of the stomach was such as to lack actual proof of the condition, but it furnished a number of clinical, laboratory and anatomic characteristics which collectively justified the diagnosis

We recalled our case of 1925, and reviewed it in the light of our revised impressions. As a result of this more recent study, we were disposed to consider the case as one of gastric syphilis and to submit the facts regarding it in some detail in order to give the reader an opportunity to weigh the evidence and to judge for himself. The clinical and laboratory characteristics of gastric syphilis are dealt with sufficiently in systems of medicine and in textbooks on diseases of the stomach to render a discussion here superfluous. The character of the anatomic changes in the stomach do not differ in any great essential from tertiary syphilitic lesions elsewhere, except, perhaps, that there is a greater tendency toward ulceration which presumably is due to mechanical trauma and to the digestive action of the hydrochloric acid and pepsin when present.

SIMULTANEOUS NONSURGICAL DRAINAGE OF THE GALLBLADDER AND INTRAVENOUS CHOLECYSTOGRAPHY*

H L BOCKUS, M D

AND

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PHILADELPHIA

There has been ample experimental proof of the ability to obtain bile from the gallbladder of animals, after certain substances have been instilled into the duodenum. Experimental evidence on man was first supplied by Silverman, and more recently by Lake and by Lyon and others. An extensive experience with duodenal bile drainage convinced us several years ago that a considerable amount of bile could be drained from the gallbladder by the method introduced by Lyon. In order to present further evidence of this fact, it was decided to carry out the following experiment. Twelve patients, whom we considered to be free from disease of the gallbladder, were studied. Each was given tetraiodophenolphthalein intravenously at 9 p. m. after a fat meal of cream and milk had been ingested at 5:30 p. m. The gravity method was used. Three and five tenths grams of the dye dissolved in 100 cc. of physiologic sodium chloride were injected. Severe reactions did not occur. Five patients experienced slight nausea or dizziness for a short time after the injection. Pictures were taken at 9:45 the following morning. This work was carried out in the roentgen-ray laboratories of Dr. George Pfahler, at the Graduate Hospital.

The technic was uniform throughout the experiment. The plate target distance, central ray focus, factors of exposure, position of patient and development were identical in the examination of each patient. Immediately after this preliminary picture was exposed, a duodenal tube was passed. Three cases were discarded. In one, the gallbladder could not be visualized, and it was not possible to intubate the duodenum in two others. In the remaining nine cases, stimulating solutions were introduced into the duodenum, and subsequent x-ray exposures were made. Ninety cubic centimeters of a 33 per cent saturated solution of magnesium sulphate¹ was the first stimulating

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* Presented in the discussion of papers on the "Combined Studies of the Gallbladder by Nonsurgical Drainage and Roentgenography," by Dr. Lyon and Dr. Cole before the American Gastro-Enterological Association, May 1, 1928.

1 The percentage of magnesium sulphate solution throughout the discussion refers to "volumetric."

solution used in each instance. In all except two cases a second stimulant, 90 cc of a 50 per cent solution of magnesium sulphate being used, was applied to the duodenum before the second cholecystogram was taken. In two of the nine cases, a 50 per cent solution of magnesium sulphate was again used, and a third cholecystogram was made. In three, a stimulation of 50 per cent solution of magnesium sulphate was followed by the intraduodenal instillation of 1 ounce of warm olive oil before the third cholecystogram. In the remaining four, olive oil alone was used after the second cholecystogram, and a third cholecystogram was taken as soon as a satisfactory drainage of bile occurred. Immediately

Results of Experiments of Obtaining Bile from the Gallbladder by Stimulation of the Duodenum

Name	X-Ray, Film 1		Stimulant		X-Ray, Film 2		Stimulant	X-Ray, Film 3		Stimulant	X-Ray, Film 4 (After Fat)	
	Size, Mm	Density			Size, Mm	Density		Size, Mm	Density		Size, Mm	Density
J H	70-33	1	33	32 N B	74-33	1	0 0	65 M B	58-19	1	Not visual	
D K	53-26	4	33	50 Y			50	0				
			50	80 L B	41-22	3	0 0	24 M B	28-10	±	Not visual	
L S	56-25	3	33	0			0 0	30 Y	41-26	±	30-16	1
			50	20 L B	41-25	2						
F B	92-35	4	33	25 L B			0 0	60 D M B	66-24	2	75-29	3
			50	50 O B	80-34	3						
T D	56-21	3	33	30 M B	41-29	0	50	0				
							0 0	40 M B	36-27	2	36-15	1
B C	70-23	4	33	60 Y			50	33 M B	50-18	2	44-10	2+
			50	70 M B	58-22	3						
A J	61-19	4	33	50 M B			50	55 M B	22-10	3	10-5	3
			50	32 L B	31-17	4						
S W	83-45	3	33	22 M B			0 0	20 D O G	57-18	±	59-20	±
			50	77 M B	68-24	2						
H M	69-28	1	33	70 B	65-42	1	50	60 Or			42-18	2+
							0 0	10 B	50-24	2		

Size first column is the greatest length and second the greatest width. Density grades 1, 2, 3 and 4. Stimulant stimulating solution introduced into the duodenum, 33 = 33%, and 50 represents volumetric percentage of magnesium sulphate solution, 0 0 = 30 cc of olive oil. Bile (cc) letters refer to color of bile obtained. N B indicates normal brown, Y, yellow, L B, light brown, O B, orange brown, M B, mahogany brown, B, brown, D M B, dark mahogany brown, D O G, dark olive green, Or, orange.

following the third cholecystogram, the duodenal tube was removed and a fat meal, consisting of a glass of equal parts of milk and cream and one raw egg, was administered by mouth. One hour later, a fourth cholecystogram was made. The first cholecystogram on the first patient was taken at 9 30 a m, and the last exposure on the last patient was completed at 4 p m. The total time taken for the experiment including pictures before the tubing, duodenal intubation with drainage, subsequent exposures of the gallbladder and the administration of the fat meal with cholecystograms one hour later was six hours and twenty-five minutes. The results of this experiment are statistically recorded in the accompanying table, and graphically illustrated by one case (A J).

In the first column of the table is the measurement of the length and width of the gallbladder shadow as depicted by the first cholecystogram. In the second is the grade of density of the gallbladder shadow. The figure in the next column represents the percentage of magnesium sulphate solution used. This is followed by the amount and color of bile



Fig 1—Cholecystogram of A J before stimulation. The gallbladder shadow is 61 by 19 mm. The density grade is 4.

obtained. The size and density of the gallbladder shadows after stimulation are then recorded (x-ray film 2). In all except two cases following this first series of stimulations with magnesium sulphate, the size of the gallbladder shadow had definitely decreased. The gallbladder in these two cases (J H and H M) was only faintly visualized before drainage,

and only one stimulant of 33 per cent magnesium sulphate was used. A decrease in the density of the gallbladder shadow occurred in five of the nine cases following stimulation with magnesium sulphate. We may conclude from the comparative study of the x-ray films before and after stimulation with magnesium sulphate that (1) intraduodenal instilla-



Fig 2—Cholecystogram of the duodenal tube of A J , showing marked reduction in size after two instillations of magnesium sulphate. The gallbladder shadow is 31 by 17 mm , the density grade 4

tion of magnesium sulphate causes a prompt reduction in the size and usually in the density of normal gallbladders, and (2) a 50 per cent solution induces a better evacuation of the contents of the gallbladder than a 33 per cent solution

SECOND SERIES OF STIMULATING SOLUTIONS

In cases B C, and A J, 50 per cent of a saturated magnesium sulphate solution was repeated, and further reduction in both the size and the density of the shadow of the gallbladder was accomplished (x-ray film 3). A repetition of the magnesium sulphate stimulant in cases



Fig 3—Cholecystogram of A J, showing marked reduction in size after the instillation of a 50 per cent solution of magnesium sulphate. The gallbladder shadow is 22 by 10 mm, the density grade 3.

D K and T D did not cause any further appearance of a "B" fraction. Olive oil was then used, and that there was further reduction in both size and density of the shadow is evident from x-ray film 3. In case H M, 60 cc of orange bile (some "B" fraction) followed the use of

magnesium sulphate, and the intraduodenal instillation of olive oil caused an evacuation of only 10 cc of brown bile, in spite of this scant flow of "B" bile, the gallbladder was considerably reduced in size on x-ray film 3. In the second series of stimulations, olive oil alone was applied to the duodenum in four cases. In all except one

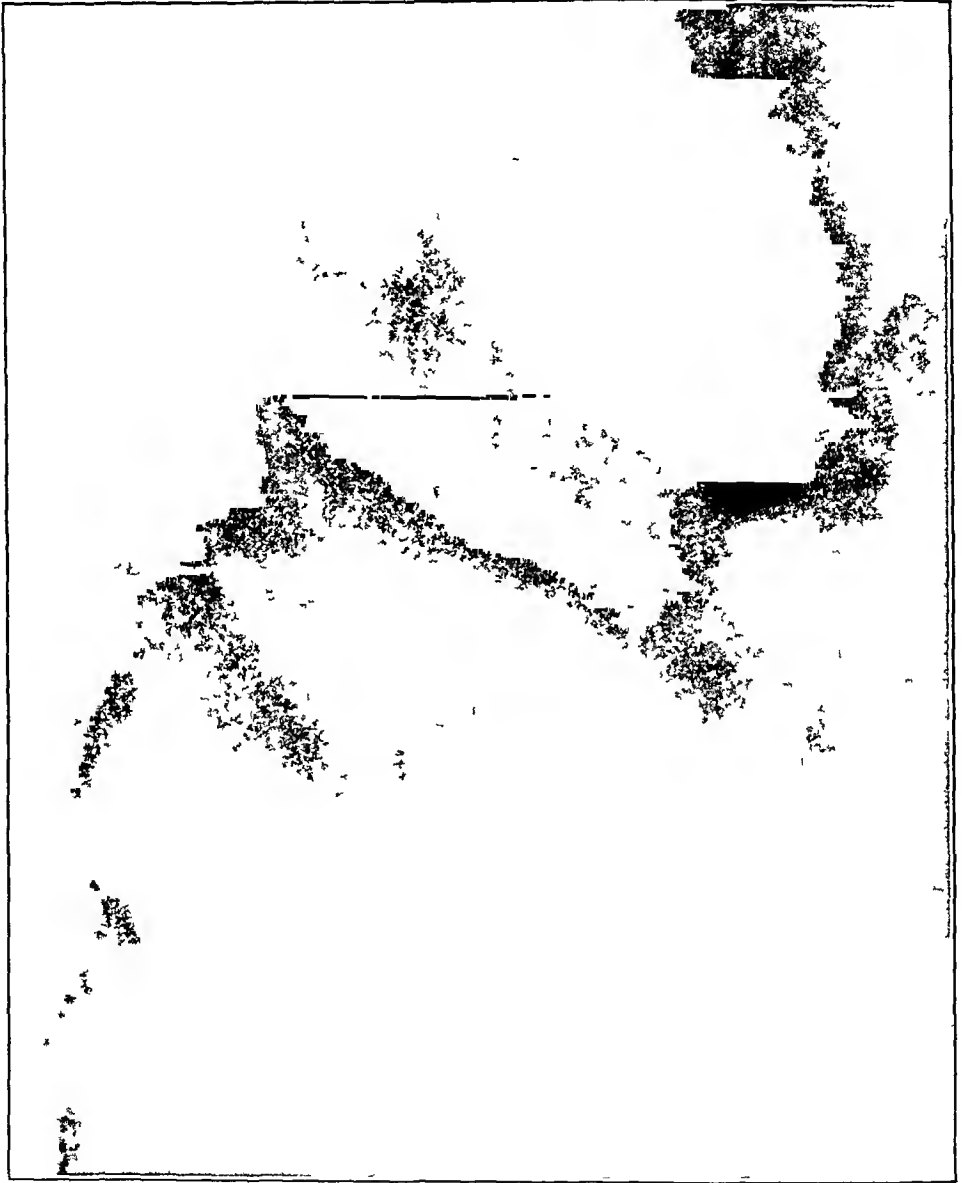


Fig 4—Cholecystogram showing still further reduction after a fat meal. The shadow is 10 by 5 mm, the density is the same as that of figure 3.

case, the third x-ray film showed a further reduction in the size of the gallbladder as compared to the x-ray films taken after stimulation with magnesium sulphate. In the exceptional case (L S), the density of the gallbladder was so reduced as to be scarcely visible. In every

case except this one, the second series of duodenal instillations caused a further reduction in the size of the gallbladder. Since this shadow was markedly reduced in density and maintained the same size, it is obvious that the stimulating solution caused further evacuation of the contents of the gallbladder in every case. The density was decreased in all cases except J H and H M, these cases were only faintly visualized at the start (possibly diseased gallbladders). In case S W, the gallbladder was large, well-visualized and filled with stones. Nevertheless, it was markedly reduced in size by drainage and the outline became faint after two stimulations with magnesium sulphate and one with olive oil. A study of the bile and cholecystograms, after a second series of stimulating solutions applied to the duodenum, reveals the following:

- 1 The gallbladder can be further reduced in size after a second or third stimulating solution is used.
- 2 The failure to obtain a dark fraction of bile on one occasion does not necessarily mean that the gallbladder has not partially emptied its contents. It seems probable that in some cases a considerable amount of the bile which enters the duodenum passes on down into the intestines. In most instances, however, the amount of "B" bile recovered seems commensurate with the reduction in the size and density of the gallbladder shadow.
- 3 Olive oil is slightly more efficient as a stimulant to the flow of bile from the gallbladder than magnesium sulphate.
- 4 The gallbladder was not completely emptied after intraduodenal instillation of magnesium sulphate or olive oil in any case.
- 5 Considering both the size and the density of the shadow, the emptying of the gallbladder after bile drainage was greater than one half its contents in seven of nine cases. The remaining patients may have had diseased gallbladders, as the original shadow was faint.

An interesting comparison is that between the third x-ray film taken after bile drainage had been completed, and the fourth taken one hour after a fat meal. It will be noted that in two cases (F B and S W) further reduction in size or density of the gallbladder shadow was not accomplished by a fat meal. In fact, the shadow was slightly larger in both cases. Of the remaining seven cases, the gallbladder shadow after the fat meal was smaller in five and had disappeared entirely in two. On the whole, the reduction after a fat meal was not as great as we had anticipated. If it is fair to judge from this small series of cases, about 30 per cent of gallbladders will be emptied as well by the duodenal tube method as by an oral fat meal. This may not represent a true percentage, as the fat meal was used after the gallbladders had been markedly reduced in size as a result of biliary drainage. In four cases, the density of the gallbladder was greater, and in two cases it was the same as the density of the shadow before the fat meal. The explanation for this is not clear.

CONCLUSION

Simultaneous duodenal bile drainage and cholecystography were carried out in nine cases. A marked reduction in the size of the gallbladder shadow occurred after medical bile drainage in every case. A decrease in the density occurred in all except two cases, one of these did not become less dense after a fat meal. The stimulants used in the duodenum were 33 and 50 per cent solution of magnesium sulphate and olive oil. Their effectiveness as gallbladder evacuants is about in the order given, the 33 per cent solution of magnesium sulphate being least effective and the olive oil most effective. The gallbladder was not completely emptied by this method in any case. Taking into consideration the size and density of the shadow, in seven cases the emptying was more than one-half. At the completion of bile drainage, the administration of a fat meal by mouth brought about further evacuation of the contents of the gallbladder in seven of nine cases. No further change occurred in two of the cases. The amount of "B" bile recovered after stimulation was commensurate with the reduction in the size and decrease in density of the gallbladder shadow in most instances. We estimate that medical bile drainage properly conducted will evacuate the gallbladder as well as a fat meal by mouth in 30 per cent of cases and that it will cause an appreciable drainage of bile from a normal gallbladder in practically every case.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

III AGE FACTOR IN THE PRODUCTION OF BRADYCARDIA*

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Since Rohrig's¹ fundamental work, which was based on the observation of a slow pulse in jaundice, the reaction of the heart to bile has been the subject of numerous investigations. Acute experimental work with the biliary constituents has constituted the bulk of research on the cardiovascular effects of bile. Important as such contributions may be, the effects produced by suddenly crowding into the circulating blood certain of the bile constituents, and that of gradual absorption into the blood and tissues of these and other products following obstruction to the flow of bile in its channels may not be identical, although the patterns of response in either case, particularly with reference to the bradycardia, may in some way be similar.

METHODS

This study extended over a period of two years. Five litters of puppies, a part of a sixth litter and six adult dogs, in all thirty-five animals, were studied, observations being made on only one litter at a time. The puppies were between 4 and 7 weeks old at the start of the experiments. The adult animals were healthy and free from mange. Jaundice was produced in the animals by ligation and division of the common bile ducts under ether anesthesia. In all but one litter, several mates on which operation was not performed served as controls.

The heart rate of the animals was taken twice a day with a Bowle's stethoscope placed over the precordium. Control rates were observed over a period of between five and fifteen days. This procedure was adopted in two litters throughout the obstructive jaundice and up to the time of the animals' death, and in the others for not more than fifteen or twenty days after the ligation and division of the common bile duct, when they were used in other experiments. A uniform method of taking the pulses was adopted. The pulse was counted only after the animals lay reasonably quiet in the lap for a minute or two. It was taken about one hour after each of the two meals, in the morning and in the afternoon. The pulse rates were counted from the second hand of a watch. Repetition of the performance gave a more than fair degree of accuracy.

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* This work was conducted in part under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

* Read before the American Physiological Society, Ann Arbor, Mich., April 13, 1928.

1 Rohrig, A. Ueber den Einfluss der Galle auf die Hertz Tätigkeit, Arch d. Heilk. 4: 385, 1865.

Electrocardiograms were made of the puppies from three of the litters before and after jaundice was produced. In one litter they were made almost daily for the first ten or twelve days following obstruction, subsequently, the interval varied between three and ten days. In the second litter, the intervals between tracings were from three to twenty days. The effects of atropine were noted in a third litter.

Blood calcium determinations² were made on all the puppies at ten to fourteen day intervals. The weight of the animals were recorded every three days.

Twice a day, the animals were given a well balanced diet consisting chiefly of meat, bread, dog biscuit, cooked vegetables and milk. Two litters were kept in 3-foot square cages. The other puppies were allowed to run free in a room. The animals that developed mange or apparent postoperative infections were excluded from the series.

In another group of experiments on decerebrated frogs, simultaneous kymographic and electrocardiographic tracings were made of the suspended heart, in which were noted the effects of the sudden release of bile from the gallbladder after its incision. As bile did not prove to be an acute peritoneal irritant to the frog, it was usually allowed to spill into the peritoneum. In another set of experiments, the common bile duct of the frog was ligated and divided under ether anesthesia, and the abdominal wall was subsequently sewed up. From one to ten days later after the animal was decerebrated, kymographic tracings were made of the suspended heart. The hooked projections of an ordinary burr were used to attach the heart to the lever.

RESULTS

A marked slowing of the heart action occurred in all the puppies soon after jaundice was produced by ligation and division of the common bile duct. By the second or third day, in almost every instance, the heart rate was slowed between thirty and fifty beats or more per minute. Bradycardia in the adult jaundiced animal, however, was not encountered in any instance.

In the puppy, the most acute slowing of the heart rate usually occurred during the first five days after obstruction. The pulse rate became progressively slower from this time to the twentieth or thirtieth day, when it usually reached its lowermost level. After this, there was an acceleration of the heart, the acuteness of which almost paralleled that of the slowing seen in the initial stage of the obstruction. In the plotted curve (fig 1) of the mean pulse rate, a series of rather acute rising peaks, with a tendency toward increased heart rate, are noted immediately following the initial bradycardia. This period I have designated as one of relative tachycardia, although the heart rates were considerably slower than those of the nonjaundiced control litter mates. It extended roughly from the twentieth to the sixtieth day of obstruction. Afterward the heart rate of the icteric animal overtook that of the control litter mate, on which operation was not performed, the rate

² Kramer, B, and Tisdall, F. F. A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serums and Plasma, *Bull. Johns Hopkins Hosp.* 32:44 (Feb.) 1921.

of the control animal had become slower as the result of age and growth. Throughout the remaining period of obstruction, the heart of the jaundiced animal, although it tended to become somewhat slower, continued to beat more rapidly than that of the nonjaundiced one. The last period was, therefore, designated one of absolute tachycardia.

The trend of the heart rate of puppies subjected to ligation and division of the common bile duct was such, therefore, as may be conveniently divided into three periods (1) one of a marked initial bradycardia, (2) that of relative tachycardia and (3) that of an absolute tachycardia.

During the first ten days or more of obstruction, the activity of the animal operated on was but slightly diminished as compared to that

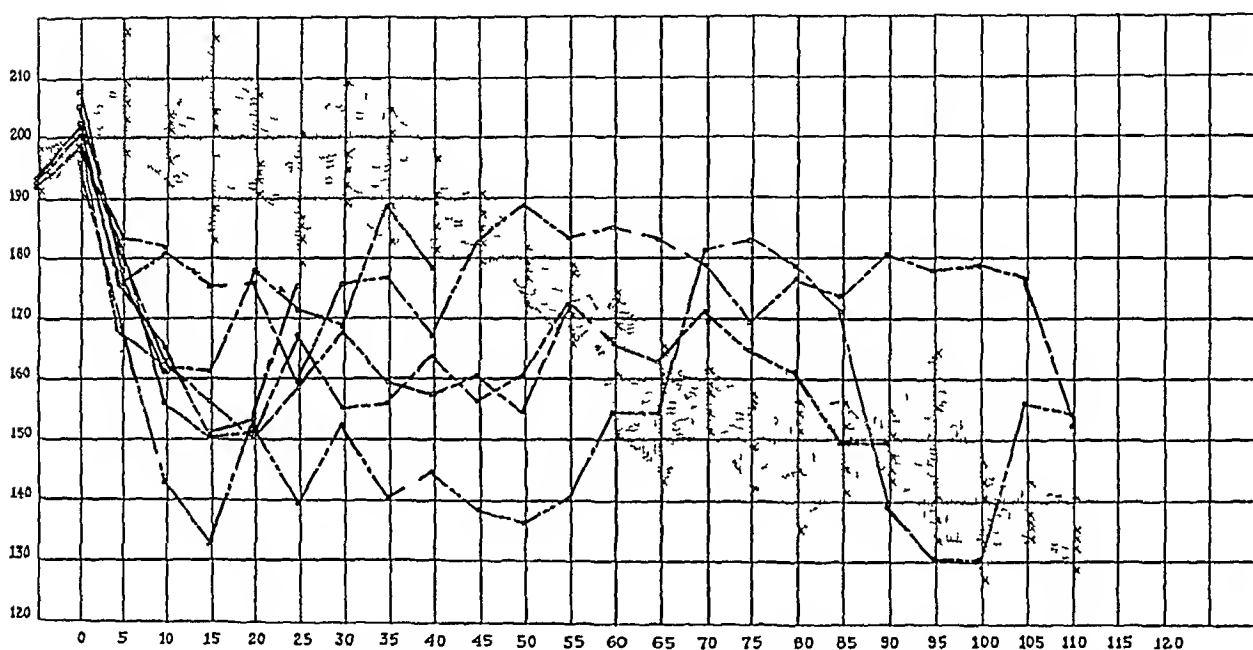


Fig 1—Plotted curve showing the characteristic trend of the heart rate of puppies subjected to ligation and division of the common bile ducts. The shaded area represents the trend of the heart rate of the nonjaundiced control litter mates. The ordinates represent heart rate, the abscissas, days after the induction of jaundice.

of the control litter mate on which operation was not performed. For this short period, it seemed none the worse off. Following this, there was a progressive decline in its vigor and strength; it was less active, less playful and possibly more combative than its control litter mate. Marked nutritional disturbances were evident, and the animal became pot-bellied or developed an ascites. Slight dyspnea was usually present during this second period in which a relative tachycardia was noted. During the third period of obstruction, and at the time an absolute tachycardia was present, the animal revealed cretinoid or rachitic characters, showed a central depression and eventually became cachectic.

*Daily Heart Rates of the Jaundiced Puppies and Control Litter-Mates During
the First Seventy Days of Obstruction **

Days	Litter I							Litter II						
	Preoperative Control Period						Nonjaundiced Control Litter Mates	Preoperative Control Period						Nonjaundiced Control Litter Mates
	206	212	200	190	188	204		202	186	193	190	190	191	
	178	206	206	214	196	193	216	196	182	190	204	200	210	
	202	210	196	230	206	220	226	204	192	200	198	186	190	
	185	190	176	206	208	210	210	200	198	200	200	192	200	
	208	196	192	210	218	230	224	194	186	202	186	186	192	
	206	210	198	196	204	200	214	196	200	200	190	178	196	
	193	204	196	184	212	196	204	220	224	214	222	200	208	
	190	208	192	188	196	206	212	202	200	212	198	210	204	
Ligation and Division of Common Bile Duct														
Days	Ligation and Division of Common Bile Duct							Ligation and Division of Common Bile Duct						
	198	226	188	212	194	206	192	190	190	182	184	194	208	
2	198	204	190	186	198	200	192	176	232	170	228	204	224	
3	190	180	182	184	170	230	210	172	176	166	184	184	220	
	162	168	200	170	170	194	174	166	176	158	204	202	222	
4	178	186	190	182	184	220	204	180	170	162	210	220	232	
	166	168	164	196	180	192	192	170	188	142	214	222	206	
5	156	190	180	142	176	200	200	178	178	180	214	202	228	
	140	164	168	158	180	206	202	180	156	168	208	206	210	
6	138	170	178	152	154	218	198	176	180	176	202	200	218	
	152	158	180	164	166	220	208	168	190	166	204	203	220	
7	134	178	160	138	170	212	190	186	168	180	208	224	212	
	144	180	154	162	170	228	194	170	172	168	204	212	208	
8	130	154	156	168	154	216	180	196	178	174	226	226	220	
	142	152	148	180	170	218	210	172	170	166	208	208	194	
9	170	162	160	182	156	206	220	196	142	158	174	194	164	
	180	146	160	176	164	188	220	216	172	170	218	204	210	
10	144	174	162	164	172	184	190	162	204	126	142	184	182	
	196	184	150	172	180	190	178	192	186	170	208	204	190	
11	140	140	162	152	150	180	180	160	182	164	186	188	216	
	146	188	150	156	140	192	168	168	250	152	190	180	240	
12	146	136	150	146	240	204	165	196	214	176	224	210	222	
	160	166	144	178		180	180	168		160	200	180	202	
13	130	164	154	146		198	192	188		152	198	198	224	
	140	160	142	162		200	202	190		160	200	194	206	
14	129	160	144	138		170	202	178		160	206	198	218	
	124	180	164	126		186	200	200		176	220	216	226	
15	114	134	168	148		173	168	180		178	212	212	240	
	128	150	130	162		190	212	148		154	182	188	200	
16	126	132	150	140		208	150	170		150	210	232	230	
	140	180	152	150		218	204	142		154	184	188	206	
17	150	142	156	158		200	204	202		198	232	216	232	
	152	164	160	154		220	194	160		198	208	200	200	
18	118	150	164	124		186	156	160		160	184	186	200	
	124	160	132	160		186	178	170		158	176	190	208	
19	180	124	150	132		180	170	172		152	190	200	200	
	168	160	154	164		192	190	194		170	186	200	222	
20	180	146	146	162		212	194	180		182	186	200	222	
	162	150	140	144		190	204	182		180	194	182	200	
21	144	160	164	150		198	192	172		178	184	182	200	
	140	154	152	176		186	114	180		194	196	172	188	
22	126	166	160	150		164	170	170		202	208	180	208	
	138	168	176	160		170	190	180		190	190	188	210	
23	146	146	168	162		200	210	142		166	166	190	202	
	148	156	156	160		190	212	172		170	172	206	190	
24	134	134	164	138		196	184	142		156	184	180	190	
	146	160	170	156		142	180	172		184	214	196	220	
25	154	156	160	172		180	182	120		126	160	160	180	
	150	154	172	180		200	200	152		166	198	210	212	
26	114	172	180	164		174	150	172		168	192	190	214	
	130	164	160	160		170	170	166		190	146	160	194	
27	154	178	170	158		206	200	182		164	194	210	218	
	144	166	160	160		208	198	182		162	198	190	202	
28	150	164	168			180	194	184		172	208	200	210	
	170	170	140			182	180	162		160	200	208	192	
29	182	164	174			214	174	158		160	188	206	206	
	170	170	144			206	198	174		150	158	174	190	
30	156	164	162			186	190	170		168	180	176	232	
	156	164	138			176	186	196		176	200	218	206	
31	148	164	132			190	194	184		174	186	190	200	
	158	164	160			200	186	170		190	210	200	202	
32	152	162	166			200	180	156		180	188	190	192	
	156	156	140			204	190	166		184	206	200	188	
33	130	160	152			216	184	180		170	200	216	212	
	140	158	144			188	192	160		198	210	192	214	

* The rates were obtained with a stethoscope placed over the precordium

*Daily Heart Rates of the Jaundiced Puppies and Control Litter-Mates
During the First Seventy Days of Observation—Continued*

	Litter I				Litter II				
	Preoperative Control Period			Nonjaundiced Control Litter Mates	Preoperative Control Period		Litter	Nonjaundiced Control Mates	
34	144	152	142	216	196	152	168	200	190
	128	152	150	180	178	170	170	188	190
35	128	172	172	208	172	204	180	208	218
	136	152	160	210	190	200	200	190	200
36	154	170	174	176	174	196	218	200	212
	132	160	158	180	170	190	220	198	194
37	144	156	170	182	168	150	182	202	200
	150	158	158	200	196	172	166	176	184
38	142	143	162	184	182	166	192	196	186
	134	162	168	200	188	170	180	200	188
39	140	132	172	160	170	170	178	200	190
	150	174	204	180	200	144	152	150	144
40	138	168	160	184	166	178	176	190	180
	150	158	146	170	164	170	168	184	202
41	152	156	138	200	196	174	186	180	190
	146	166	148	190	185	174	186	208	186
42	138	174	152	218	184	176	172	190	192
	138	168	166	194	190	152	164	192	180
43	138	158	150	190	180	180		194	176
	160	178	156	204	162	196		190	174
44	128	160	156	180	192	150		204	196
	146	168	178	200	184	172		186	180
45	138	158	184	162	188	186		180	186
	134	162	150	164	192	192		180	172
46	138	136	142	180	182	212		194	186
	148	128	164	192	174	198		184	184
47	148	128	164	192	174	176		184	184
	130	132	150	168	162	202		186	178
48	138	156	152	182	180	192		184	168
	132	170	144	200	182	190		188	174
49	140	170	174	166	150	194		184	170
	128	160	166	200	192	194		184	176
50	122	160	158	144	186	186		176	170
	130	138	172	166	186	168		176	170
51	132	180	156	172	180	190		156	164
	160	150	166	206	198	168		158	166
52	112	150	176	182	192	170		168	160
	132	152	186	176	184	190		178	170
53	140	182	190	180	190	182		142	146
	136	168	172	178	186	186		168	172
54	136	156	174	186	152	180		174	179
	144	154	166	190	172	182		158	148
55	140	162	168	172	156	186		166	158
	138	188	174	176	172	172		168	166
56	162	188	170	170	186	194		168	176
	164	208	144	174	190	198		170	172
57	132	206	154	159	168	178		170	174
	140	178	160	170	180	176		164	168
58	172	140	158	132	164	176		180	174
	172	112	160	162	154	176		170	176
59	134		170	160	180	176		192	180
	158		186	150	158	174		180	176
60	162		186	124	146	200		168	182
	164		180	160	158	200		168	178
61	166		160	128	140	200		172	164
	142		144	134	156	190		162	164
62	186		140	144	164	156		144	142
	164		152	146	162	176		160	152
63	138		150	148	166	186		156	160
	132		168	122	148	178		162	170
64	162		156	132	150	190		168	170
	146		170	138	170	206		160	168
65	150		164	138	158	182		168	166
	150		182	164	166	186		162	180
66	166		170	150	154	182		178	172
	150		180	154	150	186		180	174
67	166		200	150	146	186		170	158
	180		164	162	170	182		138	146
68	190		168	136	144	178		146	168
	176		144	150	162	160		154	160
69	180		150	174	150	192		154	166
	176		178	162	156	186		160	158
70	192		180	156	154	188		146	166
	182		174	150	152	170		156	154

Its appetite, however, often remained quite voracious although there were short intervals of marked anorexia. Marked dyspnea was present, even in the absence of effusions into the peritoneum, although these effusions may aggravate this symptom.

Respiratory variations of the heart rate were present in the normal puppy when the heart was not beating excessively fast. The electrocardiogram revealed their presence at rates of 200 or more per minute. When the heart rate was 170 or less, it was usually detected with ease by the auscultatory method. All manner of stimuli, slight movements of the body and slight respiratory irregularities occasioned abrupt transitions in the heart rate of the normal puppy. It sometimes suddenly advanced from 150 to 250 beats per minute. Readjustment with removal of the stimulus, whatever it might be, was quick. The heart was exceptionally labile and responsive. Marked activity on the part of the jaundiced puppy during the first period of obstruction was also followed by an increase in the heart rate that approximated that observed for the nonjaundiced animal. The tachycardia was usually not so marked, and it is my impression that the transition was not so rapid. Since bradycardia was established at the time of the obstruction, the differences between the minimal and maximal heart rates were, therefore, greater in the jaundiced animal. Slight respiratory irregularities in this animal did not so readily upset the established rhythm of the heart, and despite the wider range over which the heart rate of the jaundiced pup might vary in the initial obstructive period, a tendency toward fixation of the rate was noted. After thirty days or more of obstruction, the infrequency with which respiratory variations of the heart occurred, so readily noted in the animals on which operation was not performed, became more noticeable. In the later periods of obstruction, the observation of a comparatively much more regular heart and of a rhythm much less influenced by respiration was even more evident.

Gross irregularities of the heart were not detected at any time during the period of obstructive jaundice, nor did the electrocardiograph reveal them.

A study of the heart rate of the adult animal revealed the absence of slowing at any time during the obstruction. A slight acceleration of the pulse rate was usually present. The animal lived a relatively much shorter time after the induction of jaundice, the tissues became more deeply bile stained and the intoxication seemed more severe. While ascites was a common complication it occurred earlier, and autopsy disclosed it almost invariably associated with a perihepatitis and a chronic exudative peritonitis, of which the animal usually died. In spite of the marked ascites often encountered, the symptoms of dyspnea were inconspicuous or absent. The usual respiratory variations of the heart were present at all times, and they did not appear to be exaggerated.

Five minutes after atropine (1 mg per kilogram of body weight) was administered to the jaundiced and nonjaundiced litter mates, and at a time when a bradycardia was established, practically maximum heart rates (from 280 to 300) were obtained in both groups. The highest rate was noted in one of the jaundiced animals.

The blood serum calcium in puppies with obstructive jaundice fell progressively to about two-thirds the normal values before death³.

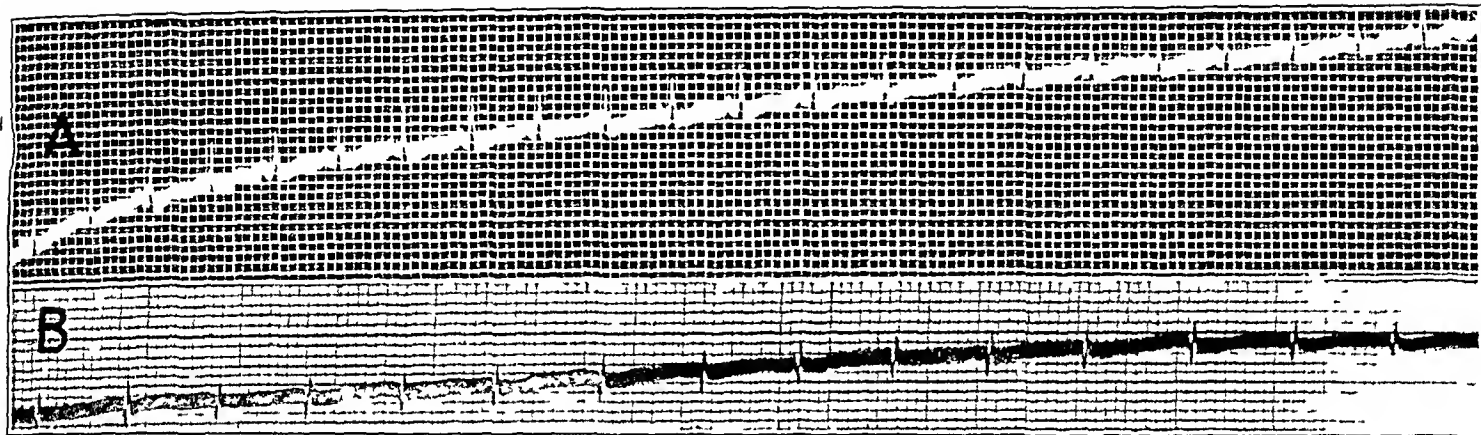


Fig 2—A, control curve, lead I, rate 210 B, curve made four days after obstruction, lead I, rate 145, low voltage. Right predominance and slight sinus arrhythmia.

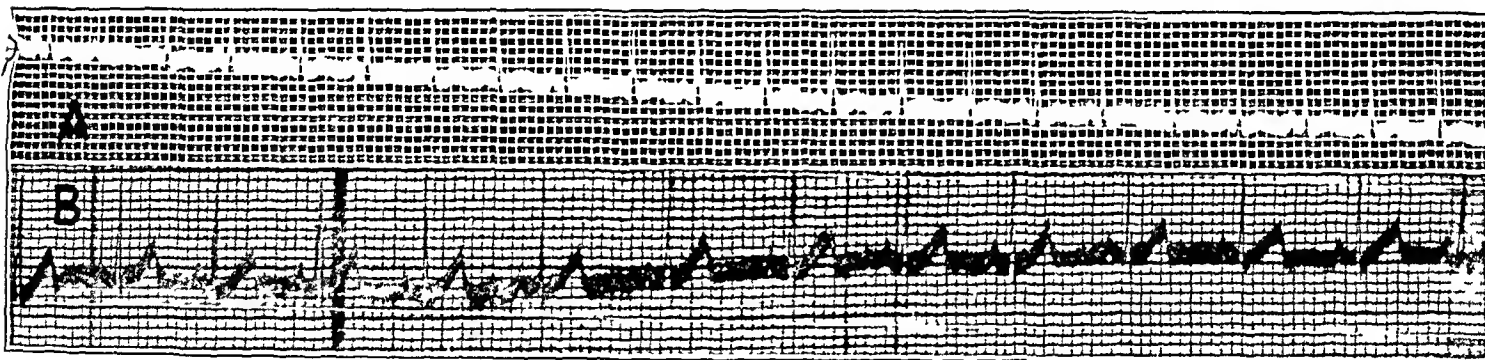


Fig 3—A, control curve, lead I, rate 217 B, curve made thirteen days after obstruction, lead I; rate 140. Slight sinus arrhythmia.

THE ELECTROCARDIOGRAM

Typical examples of slowing of the heart rate are seen in figures 2 and 3.

The most frequent abnormality encountered in the electrocardiograms of two litters of puppies comprising eleven animals was an inversion of the T-wave (fig 4). The two control animals showed a transient negativity in the first and third leads, respectively. Of the nine animals

³ Buchbinder, W. C., and Kern, Ruth R. Experimental Obstructive Jaundice I. Growth Factor in Defective Calcification, *Arch Int Med* 40:900 (Dec.) 1927.

in which jaundice was produced, six developed negativity, although the T-wave had been upright in all the control tracings except one in which it was diphasic in the first lead. In two animals, the T-wave became inverted in all leads, in another, negativity was displayed in the second and third leads. The fourth animal which had a diphasic T-wave in the first lead of the control tracing developed an inversion in this lead with diphasic T-waves in the second and third leads. The remaining two puppies of the operated series developed a T-wave negativity in the

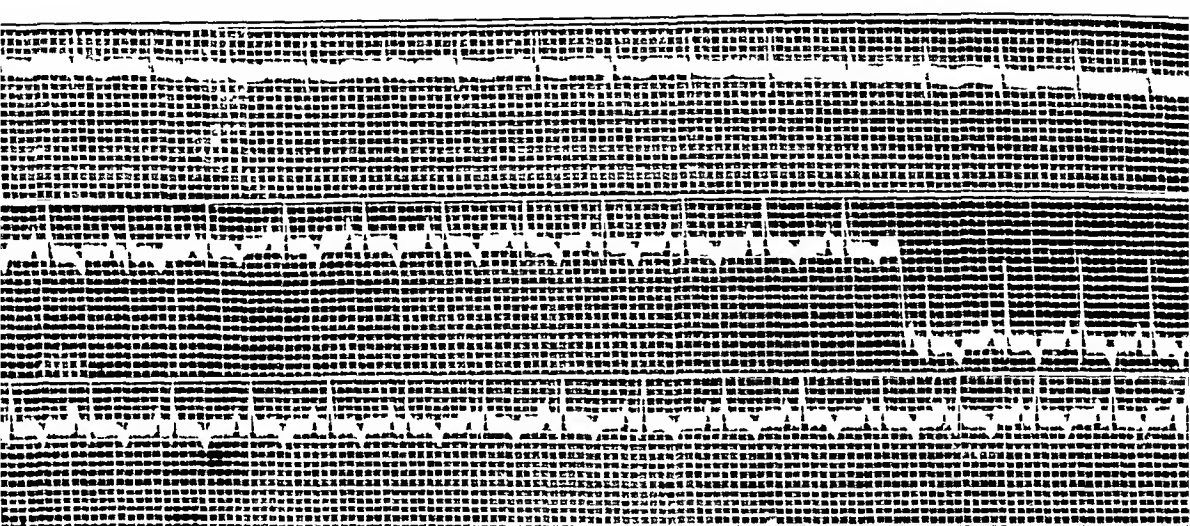


Fig. 4—Curve made 108 days after ligation and division of the common bile duct, showing inversion of the wall ledges. Average rate in all leads, 171. There is not any variation in the PR interval in any lead, in lead I it is 0.01 seconds.

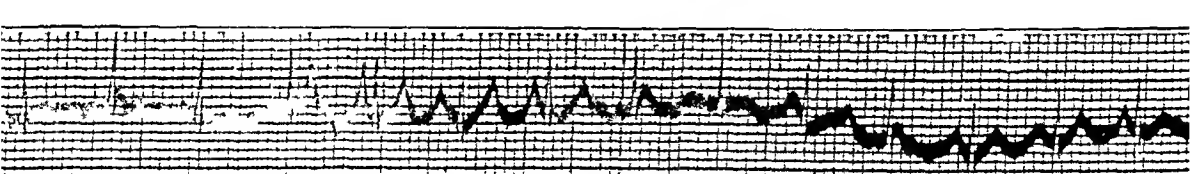


Fig. 5—Curve taken ten days after the induction of jaundice, showing a transient dislocation of the p wave.

first and third leads, respectively. The two control dogs in which jaundice was produced after their litter mates were dead also developed a negativity in the first and third leads, respectively, although the T-wave had been upright during the 100 days or more during which they served as controls. The latter were studied for but a short time after the induction of jaundice. Including the three animals in which a diphasic T-wave was noted in one of the leads, negativity was observed in eight of the eleven puppies subjected to ligation and division of the common bile duct.

The time at which negativity was disclosed after this operation was variable, and ranged between the third and sixty-fifth day. Two points, however, are worthy of mention. (1) Negativity was transient in most cases and it was not a permanent feature for any length of time except in a few instances. Even in those instances in which it may have been noted in several successive tracings, at the time of death the T-wave was upright. (2) T-wave negativity developed early (in from three to ten days) after the ligation and division of the common bile duct in nearly half the number of animals studied electrocardiographically, and at some time prior to that when they evidenced cardiac embarrassment and damage, in the tachycardia, dyspnea and muffling of the heart tones.

The electrocardiogram does not reveal in any instance a prolongation of the PR interval. Aberrant QRS complexes were not observed, and the time occupied by them was not lengthened. Transient dislocation of the pacemaker was encountered in one animal ten days after the induction of jaundice (fig 5). Although more than half the number of jaundiced puppies developed ascites, transient right ventricular preponderance was found in only one instance.

REFLEXES FROM THE GALLBLADDER TO THE HEART IN THE FROG

Incision into and release of bile from the gallbladder of the decerebrated frog produced almost invariably a sudden marked slowing of the heart rate, with a markedly increased force of the beats. It was possible to prolong this action over a period of fifteen minutes or more, before the normal rhythm was reestablished. Typical reflexes following this operation are shown in figure 6. Destruction of the medulla, decapitation or atropinization prevented the reflex or abolished it at once. Simultaneous electrocardiographic and kymographic tracings revealed some striking changes. Apart from the marked slowing due to sinus block (fig 7) a sudden inversion of the T-wave was frequently seen (fig 8). Acute distention of the gallbladder or cannulated common bile duct also produced a similar reflex, but usually of shorter duration. Marked distention of the gallbladder occurred in frogs which had had their common ducts ligated and divided for several days. In these frogs, spontaneous arrhythmias and sudden halving of the rate were frequently observed.

COMMENT

There has been a common understanding for many decades that a slow pulse rate is one of the usual accompaniments of obstructive jaundice, and in most modern textbooks of medicine one finds much, and

REMOVAL OF NORMAL TENSION
OF GALLBLADDER BY INCISING

A

GALLBLADDER
INCISED

ELECTROCARDIOGRAM
OFF



B

RELEASE OF NORMAL TENSION
IN GALLBLADDER BY INCISING

$\frac{1}{600}$ GR ATROPINE CRURAL LYMPH SAC



C

$\frac{1}{500}$ ATROPINE CRURAL LYMPH SAC

INCISING GALLBLADDER

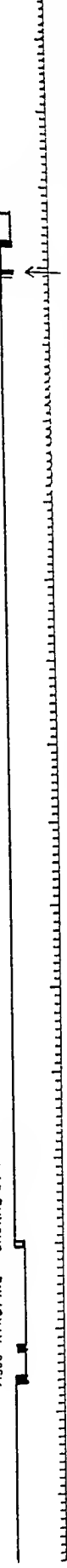


Fig 6—Typical cardiac responses following incision into and release of bile from the gallbladder in the decerebrated frog. Following the incision there is usually a slight latent interval before the reflex is produced. In A the transient acceleration just prior to that of marked slowing should be noted. In B the rate is restored after the administration of atropine. In C the reflex is prevented by previous atropinization.

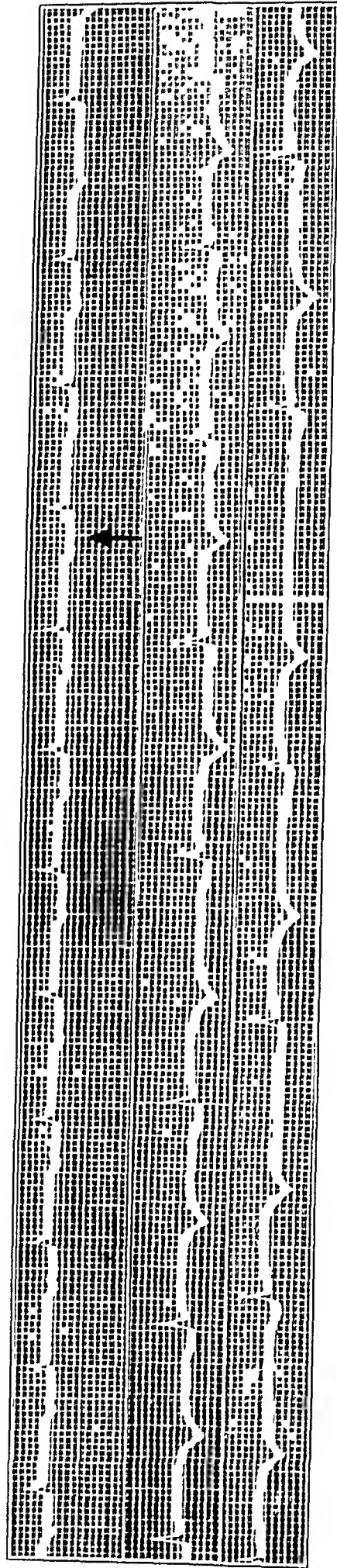


Fig 7 —Continuous tracing showing sinus block and the inversion of the T-wave in the frog after the incision into and release of bile from the gallbladder The electrodes were placed at the base and apex of the suspended heart

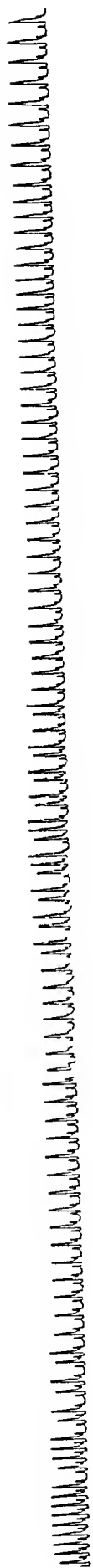


Fig 8—Showing types of spontaneous arrhythmias that develop in frogs in which the common bile ducts were, for several days, previously ligated and divided. In the two lower tracings the common duct was tied for seven days. In the upper tracing there occurs a transient halving of the rate.

perhaps undue prominence given this symptom (Osler and McCrae,⁴ Elliott,⁵ Porter,⁶ Allbutt,⁷ Rolleston⁸ and Umber⁹) A perusal of the literature, however, reveals important exceptions Mackenzie¹⁰ had never seen this symptom, although he had looked for it Vaquez¹¹ stated that if a slowing of the heart occurs it is scarcely appreciable, in the experience of McVicar and Fitts,¹² bradycardia in jaundice "proved almost a myth" Windle¹³ noted that in the vast majority of cases of obstructive jaundice the frequency of the heart was about or above the normal, but that catarrhal jaundice in young people was commonly associated with a slow pulse rate The observations I have made on dogs are in harmony with those of Windle

In the large literature dealing with the cardiovascular effects following the injection of bile constituents or whole bile, there is the strong evidence that the vagus plays some rôle in the slowing of the heart rate To assume that a similar mechanism is operating in the intact, unanesthetized animal in which jaundice has been induced by ligation of the bile duct would be gratuitous Granted, even, that they are similar, the basic experimental conditions are of a different nature, for in the former a state of jaundice, which implies a discoloration of the skin and mucous membranes, is not present Moreover, such mechanical factors as may arise from acutely or chronically distended bile passages are necessarily obviated in the first type of experiment It was customary in the past to attribute most forms of slowing of the heart rate to a vagus action, and in this respect jaundice does not form an exception In view of the fact that the factor of age is definitely known to influence

4 Osler and McCrae *Modern Medicine*, Philadelphia, Lea & Febiger, 1926

5 Elliott, C A, in Tice, Frederick *Practice of Medicine*, Hagerstown, Md, W F Prior Company, 1925, vol 7, p 227

6 Porter, L A, in Ab, I A *Pediatrics*, Philadelphia, W B Saunders Company, 1924, vol 3, p 645

7 Allbutt, C A *A System of Medicine*, London, The Macmillan Company, 1909, vol 6

8 Rolleston, H *Diseases of the Liver, Gall Bladder and Bile Ducts*, London, the Macmillan Company, 1912, p 543

9 Umber, F *Erkrankungen der Leber und der Gallenwege*, Handbuch der Inneren Medizin, Berlin, Julius Springer, 1918, p 23

10 Mackenzie, J *A Study of the Pulse*, London, The Macmillan Company, 1902, *Diseases of the Heart*, London, Oxford Medical Publications, 1921

11 Vaquez, H *Diseases of the Heart*, trans by G F Laidlow, Philadelphia, W B Saunders Company, 1924

12 McVicar, C S, and Fitts, W T *Clinical Aspects of Jaundice*, J A M A 89 2018 (Dec) 1927

13 Windle, J D *The Heart's Action in Jaundice*, Brit M J 1 123 (Jan) 1916

the frequency of certain phenomena which have a vagal origin,¹⁴ the observations that I have made on dogs would lend support to the vagal hypothesis of bradycardia in jaundice

Apart from such indirect evidence, that furnished by the atropine test would indicate that in obstructive jaundice in puppies the original vagal tone is intensified. The absence of bradycardia in the adult dog could be explained on the basis of a less sensitive vegetative nervous system. The absence of any gross irregularity of the heart rate at the time of the slowing in puppies need not preclude a vagus action, Lewis¹⁵ pointed out that the criterion of irregularity, although valuable, may not be absolute. It is conceivable also that the absence of respiratory variation of the heart rate may be due to increased vagal tone, since this form of arrhythmia may be regarded as evidence of an insignificant instability of tonic nerve action. An exaggeration of this phenomenon would more easily fit in with the accorded explanation. A selective action of one of the bile constituents on the sinus part of the genetic system is possible, but such is not afforded by the electrocardiogram. The PR interval was not prolonged in any case, and a change in the configuration of the P-wave was encountered in only one instance. While the inversion of the T-wave of the electrocardiogram obtained in frog experiments appeared to have a vagal origin, that noted in the puppies cannot so readily be conceded to have such a derivation. In the frogs, the electrodes were placed on the basal and apical portions of the heart, and Lewis, Meakins and White¹⁶ called attention to the fact that one cannot be too circumspect in interpreting curves taken by direct leads. The appearance of the invert form so early after obstruction of the bile ducts in half the series studied electrocardiographically, its transitoriness and the reappearance in the electrocardiogram in the one animal at about the time of reestablishment of bile flow to the intestine suggest a functional origin, and not one due to structural change in the heart muscle

14 Gilbert (Gilbert, N. C. The Increase of Certain Vagal Effects with Increased Age, *Arch Int Med* **31** 423 [March] 1923), found that a marked slowing of the heart rate could most readily be produced in adults, especially in the sixth decade, and noted the infrequency of its occurrence in youthful subjects. Hering (Hering, H. E. *Die Karotissinusreflexe auf Herz und Gefasse vom normal-physiologischen, pathologisch-physiologischen und Klinischen Standpunkt*, Dresden and Leipzig, Theodore Steinkopff, 1927), however, pointed out that the vagus trunks in the neck are resistant to mechanical stimulation and that this reflex is due to a specific reflex. The focus for the sensory nerve distribution is what Hering calls the "carotid sinus."

15 Lewis, Thomas. *The Mechanism and Graphic Registration of the Heart Beat*, London, Shaw & Sons, 1925, p. 433.

16 Lewis, T., Meakins, J., and White, P. D., *The Excitatory Process in the Dog's Heart. I. The Auricles*, *Phil. T. Roy. Soc., London* **205** 375, 1914.

The mechanical factor produced by acute and even more chronic distentions of the intrahepatic and extrahepatic ducts, particularly the sudden changes of intraductal pressure, have, up to the present, not received any consideration as a cause for the bradycardia in jaundice. I am of the opinion that this factor and possible injury of the liver produced in obstruction but particularly the former may play an exceedingly important rôle in furnishing a focus for the sensory nerve distribution of a part of the specific reflex, and acting through the vagus. Not only may such mechanism be contributive in initiating or maintaining a slowing of the heart rate in obstructive jaundice, but it may also be operating in the abnormal rhythms accompanying certain cases of cholelithiasis without frank jaundice. Straus and Hamburger¹⁷ studied a group of the latter type of cases with the electrocardiogram.

In their studies of the visceral sensory nervous systems, Carlson and Luckhardt¹⁸ did not readily obtain cardiac standstill in the frog by means of electrical or mechanical stimulation. They noted the complete and almost instantaneous inhibition following the mere touching of the urinary bladder and small intestine. Sherrington¹⁹ pointed out that the main function of the receptor is to lower the threshold of excitability of the arc for one kind of stimulus and to heighten it for others. "It is necessary that the mechanical stimulation be adequate, and to be adequate it must be of a certain kind." The cardiac reflexes which I provoked in the frog by producing sudden changes in the intraductal pressure, following the release of bile after incision of the gallbladder, appear to be analogous to the vascular reflexes which Sherrington²⁰ strikingly provoked by mechanical distention transiently produced by the injection of a few cubic centimeters of saline solution into the bile ducts. This regularly evokes a marked rise of arterial pressure. Also, the early bradycardia that I noted in puppies, following the ligation of the common duct, could be explained on a similar basis, in light of the recent investigations of Bollman, Sheard and Mann,²¹ who showed an almost immediate maximal intraductal pressure after ligation of the common duct.

17 Straus, D. C., and Hamburger, W. W. The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholelithiasis, Cholecystitis, and Duodenal Ulcer, *J. A. M. A.* **82** 706 (March) 1924.

18 Carlson, A. J., and Luckhardt, A. B. Studies of the Visceral Sensory Nervous System. V. Cardiac and Vasomotor Reflexes Induced by Visceral Stimulation in Amphibia and Reptilia, *Am. J. Physiol.* **55** 31 (Feb.) 1921.

19 Sherrington, C. S. Integrative Action of the Central Nervous System, New York, Charles Scribner's Sons, 1906, p. 12.

20 Sherrington, C. S. On the Spinal Animal, Marshall Hall Prize Address, *Med.-Chir. Tr.*, 1899, vol. 82.

21 Bollman, J. L., Sheard, C., and Mann, F. C. An Experimental Study of Obstructive Jaundice with Particular Reference to the Initial Bilirubinemia, *Am. J. Physiol.* **80** 461 (April) 1927.

The same authors also demonstrated an early functional incapacity of the hepatic cells in the transference of bile pigment from the vascular capillaries into the bile capillaries. One must, therefore, also consider injury of the liver in jaundice as a possible cause for the slowing of the heart rate.

The early necrosis of hepatic cells after obstruction of the common duct was emphasized by Ogato²². Finsterer²³ called attention to the symptom bradycardia as being almost pathognomonic of injury to the liver. This problem, carried by him into the laboratory, yielded fruitful results. He found that bradycardia could most readily be produced by experimental lesions of the liver, in contrast to the acceleration invariably noted after contusions of the intestines, spleen and other viscera. He further noted that the bradycardia was not modified by atropine or section of the vagi. Recently, Ricciuti²⁴ reported on clinical bradycardia with lesions of the liver due to contusion, bradycardia was particularly marked in two cases of gunshot wounds of the liver. Straus²⁵ also noted bradycardia in clinical cases of contusion of the liver, but was unable to get anything like uniformly positive results in his experimental work on dogs (unpublished).

Pearcy and Howard²⁶ arrived at the conclusion that cardiac reflexes provoked by mechanical stimulation of abdominal viscera (and this included the mechanical distention of the gallbladder) must be of sympathetic origin. They noted that an extrasystolic arrhythmia was obtained equally well whether or not the vagi were intact, and that when the vagi were intact and the cord was cut "so as to eliminate the sympathetic system from participating in the reflex, the irregularities were never observed." My objections to such conclusions are as follows. In the first place, transection of the cord (the authors did not mention the site of transection, which is important, but I suppose it is at a high level) profoundly alters not only the cardiac but every other physiologic mechanism. The fact that reflex responses do not occur over the vagi after this procedure is not by any means indisputable proof that they may not occur in the intact animal. The experimental animals used

22 Ogato, T. Beitrage zur experimentelle erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallenkapillaren bei der Unterbindung des Ductus choledochus unter der Ikterogenvergiftung, Beitr z path Anat u z allg Pathol **55** 236, 1913

23 Finsterer, H. Ueber Leberverletzungen, Deutsche Ztschr f Chir **118** 1, 1913

24 Ricciuti, G. Bradicardia in ferite e lesione contusive del fegato, Policlinico (sez chir) **34** 229 (May) 1927

25 Straus, D. C. Personal communication to the author

26 Percy, J. F., and Howard, H. Studies on the Visceral Sensory Nervous System XVIII Reflexes from the Peritoneal Viscera to the Heart, Am Heart J **2** 530 (June) 1927

by Peaicy and Howard not only were treated with barbital, but were given sufficient doses of barium chloride, which of itself provoked extrasystoles before mechanical stimulation was begun. Lastly, they provoked not a tachycardia which would constitute a typical sympathetic response but an extrasystolic arrhythmia which is produced capriciously and only with the greatest difficulty by sympathetic stimulation.

There has been almost unanimity of opinion that some central depression occurs in obstructive jaundice. I²⁷ attributed the amelioration of the symptoms of tetany and the delay in their appearance in the parathyroidectomized animal which had been jaundiced for some time previously to central depression. Working more recently with picrotoxin, a violent medullary stimulant, I was not able to note any appreciable differences in the time of appearance or in the pattern of the preconvulsive and convulsive seizures in the jaundiced and nonjaundiced dog, although the drug was administered to the former when there appeared to be depression. The question of depression of cardiovascular function has also been raised, and it has been customary to attribute to it not only the slowing of the heart rate, but also the slower respirations.

When bradycardia occurs in the puppy shortly after the induction of jaundice, there is but little change in the activity and behavior of the animal. Even when the animal becomes apathetic and inactive and shows depression, at least in spirits, bradycardia does not exist, and there is an acceleration of the heart. At this time, there appear to be definite evidences of cardiac failure which are manifested in the tachycardia, the presence of murmurs and the dyspnea which may occur independently of ascites. From such observations one should be unwilling to subscribe to the prevalent view that bradycardia occurring in jaundice is due to central depression.

Mention should also be made of the disturbances of the calcium metabolism that arise in obstructive jaundice, and of possible cardiac effects resulting from changes in the ionic equilibria of the blood and tissues. I have called attention to the marked decrease in the blood serum calcium in the jaundiced puppy. King, Bigelow and Pearce²⁸ suggested that so far as their quantitative studies of the calcium balance in obstructive jaundice show a marked loss of this substance from the heart muscle, the slowing of the heart rate in jaundice may be due to the removal of the stimulating force from this organ. The special

²⁷ Buchbinder, W. C., and Kern, R. Experimental Obstructive Jaundice. II. A Modification of the Tetany Mechanism in Jaundice, *Arch. Int. Med.* **41**: 754 (May) 1928.

²⁸ King, J. H., Bigelow, J. E., and Pearce, L. Experimental Obstructive Jaundice, *J. Exper. Med.* **14**: 159, 1911.

affinity which the heart discloses for calcium²⁹ in hypercalcemic states, following the use of Collip's extract, makes the question of a possible loss of calcium from the heart in jaundiced states a mooted one. It is to be noted that the initial marked bradycardia is not associated with any quantitative change in the blood serum calcium. The first evidence of the latter's decrease is concomitant with a relative tachycardia. If it is correct that at this time there is a loss of calcium from the heart muscle, I believe that any possible effects of such would be overshadowed by a direct poisoning of the heart muscle. Since the adult jaundiced dog does not manifest any significant change in the heart rate, and discloses a normally constant blood serum calcium, the question remains of great interest.

Finally, a brief consideration of the possible mechanisms involved in the production of the characteristic trend of the heart rate in jaundiced puppies must not be omitted. I have merely attempted to offer a plausible and convenient explanation to fit the facts. It is believed that the slowing of the heart rate in jaundiced puppies is a specific reflex through the vagus, and that the mechanically distended intrahepatic and extrahepatic ducts serve as a focus for visceral stimulation. The reflex slowing is unimpeded during the first five or ten days by any of the metabolites arising as a result of the obstruction. The query raised by Carlson³⁰ whether the persistence of an abnormal reflex for so long a time would be unusual constitutes, to my mind, the most valid objection to such an hypothesis. The second period, that of relative tachycardia, represents the first poisoning effects of bile (presumably the bile salts) on the heart. The acceleration, however, is more than counterbalanced by the heart slowing mechanism suggested previously, and the heart rate during a considerable period of the jaundice remains slower than in the normal animal. The third period of absolute tachycardia represents a direct marked poisoning of the heart muscle by metabolites, and this is associated with a depression and toxemia.

SUMMARY

The trend of the heart rate of puppies subjected to ligation and division of the common bile duct is such as may be conveniently divided into three periods: (1) one of an initial marked bradycardia, (2) one of relative tachycardia and (3) one of absolute tachycardia.

An inconspicuous, or absent respiratory variation of the heart rate is noted in the jaundiced puppy, especially in the middle or later periods of obstruction.

²⁹ Collip, J. B. Harvey Lectures, Baltimore, Williams & Wilkins Company, 1925, p. 142.

³⁰ Carlson, A. J. Personal communication to the author.

Inversion of the T-wave is the most common abnormality in the electrocardiogram of the jaundiced puppy. It is thought to have a functional origin rather than one resulting from organic changes in the heart muscle.

Bradycardia does not occur in the adult dog subjected to ligation and division of the common bile duct. A slight degree of acceleration is the rule. The absence of bradycardia under these circumstances is explained on the basis of a less sensitive vegetative nervous system.

Bradycardia in the puppy is unassociated with apparent marked central depression, which is characteristically present in the late periods of obstruction when acceleration is the rule.

In the decerebrated frog, there is a specific reflex from the gall-bladder to the heart. In order to evoke it, the stimulation must be "adequate." Acute changes in pressure in the bile tracts is thought to constitute an "adequate stimulus." Spontaneous arrhythmias, with sudden halving of the rate, frequently occur in the suspended hearts of frogs, which for several days have had a ligation and division of their common bile ducts.

The temptation arises to explain the initial marked bradycardia that occurs in jaundiced puppies on the basis of a specific reflex, the mechanically distended intrahepatic and extrahepatic ducts serving as a focus for visceral sensory stimulation. The reflex is thought to be through the vagus.

SECRETIN NOT A HEMATOPOIETIC STIMULANT *

J T KING, M D

MINNEAPOLIS

The present intense interest in substances thought to have a stimulating influence on blood-forming tissues again emphasizes the need for a clearly defined set of criteria by which to judge regeneration

The picture of a true regeneration is best seen following hemorrhage in the healthy animal Table 1 gives the data on two experiments in

TABLE 1—*Results of Two Experiments in Which the Blood Count in the Rabbit Was Reduced by Hemorrhage*

Experiment Number	Date	Red Blood Cells	White Blood Cells	Reticulo-cytes	Experimental Procedure
50	2/ 9	4,190,000	6,850	11	Bled 34 cc from the vein of the ear
	10	2,590,000	6,400	22	
	11	2,490,000	5,400	71	
	12	3,130,000	5,050	73	
	13	2,740,000	5,750	144	
	14	2,980,000	8,150	135	
	15	2,750,000	4,700	166	
	16	3,330,000	10,250	154	
	17	3,510,000	6,000	126	
	18	3,350,000	5,500	51	
	19	3,520,000	7,350	56	
	20	3,310,000	3,850	62	
	21	4,200,000	6,750	64	
	23	4,110,000	6,800	26	
	4/ 9	6,450,000	14,700	10	
51	2/ 9	4,520,000	10,450	25	Bled 18 cc from the vein of the ear
	10	3,570,000	9,550	26	
	11	3,920,000	11,350	74	
	12	3,570,000	8,800	101	
	13	3,580,000	16,400	84	
	14	3,379,000	10,100	84	
	15	4,100,000	9,650	75	
	16	4,330,000	6,600	72	
	17	4,180,000	9,100	52	
	18	4,040,000	7,500	50	
	19	3,960,000	10,100	68	
	20	4,270,000	6,500	58	
	21	4,320,000	8,600	90	
	23	4,810,000		51	
	4/ 9	6,370,000	13,400	12	

which the blood count in the rabbit was reduced by hemorrhage The experiments extend over the recovery period, leukocyte and reticulocyte counts are given The two points to be especially noted are that rise in red count due to regeneration is slow, and that histologic evidence of regeneration, as indicated by the rise in reticulocytes, is unmistakable Stained smears show an increase in the number of polychromatophilic cells, and when regeneration is active nucleated reds may appear

As a contrast to this picture of true regeneration, with the slowly rising count accompanied by an increase of reticulocytes and polychro-

* Submitted for publication, July 31, 1928

* From the Department of Physiology, University of Minnesota

matophilic cells, one may cite the rapid rise in count known to follow the injection of such substances as histamine or tissue extracts in general. In this case, the red count rises rapidly, reaches its maximum in most cases between one and two hours and then returns gradually to the original level. The time required for the whole reaction is relatively short, being on the average from three to four hours. If such substances are given intravenously, much less time is required. Table 2 gives data on an experiment in which 50 cc of secretin, an acid extract of intestinal mucosa, was injected intravenously into a dog under ether anesthesia. It is seen that the count rose rapidly to a maximum and then returned promptly to normal. This rapid rise and fall in red count, unaccompanied by any histologic signs of regeneration such as increase in reticulocytes or polychromatophilic cells, is char-

TABLE 2—*Results of an Injection of 50 cc of Secretin Into a Dog Under Ether Anesthesia*

Time, P M	Red Blood Cells	Remarks
3 20	7,030,000	Ether anesthesia started at 3 p m Initial high count probably due to struggle during induction of anesthesia
3 30	6,620,000	
4 08	6,540,000	
4 11	6,550,000	50 cc secretin
4 27 to 4 35		
4 40	6,480,000	
4 43	7,440,000	
4 50	7,680,000	
5 03	7,300,000	
5 17	7,030,000	Killed by chloroform
5 28	6,550,000	
5 38	6,080,000	
5 40		

acteristic of the reaction to tissue extracts. The explanation of the increase in count is not that new cells are produced, but that the blood is temporarily concentrated owing to the escape of plasma from the vascular system. The evidence on this problem will be presented.

In this study the reticulocyte count, as well as the usual smears stained with Wright's stain, was used in judging the activity of the blood-forming tissues. The reticulocyte is seen as a red cell which contains a characteristic bluish substance present in variable form and amount. Only a granule or two may be seen in some cells, while others may contain a large amount of the substance in the form of a net or filaments. This bluish substance, which is precipitated by the dye, is seen in a diffuse form in the ordinary blood smear stained with Wright's stain. The whole cell containing it is blue. This is the well known polychromatophilic cell, which has been recognized for a long time as being present in increased numbers whenever the blood-forming tissue is stimulated to increased cell production.

REVIEW OF LITERATURE

The term "reticulocyte" was suggested by Krumbhaar¹ to designate what had been referred to as the reticulated erythrocyte. At the same time, he suggested the term reticulosis to designate an increased number of reticulocytes in the peripheral blood. His paper contains data on normal counts and variations in some experimental conditions. He pointed out that the figures usually given for man are rather high, and set the normal between 0.1 and 1 per cent. It was also pointed out that the reticulocyte count in the infant soon falls to a figure close to that of the adult. Some data on laboratory animals are given.

In 1921, Key² published a work on the significance of the reticulum found in these cells and its relation to basophilic stippling and polychromatophilia. The work is comprehensive and should be read by any one interested in this subject.

The reticulocyte lends itself more readily to quantitative estimation than does the polychromatophilic cell. This is due to the fact that variations in staining technic are not so apt to influence the reticulocyte count. Then, too, the personal factor is not so important in the counting of reticulocytes, as the observer is determining the presence or absence of definite cell inclusions, while in the case of the polychromatophilic cell, one has to decide on the basis of slight differences in color caused by a diffusely distributed substance. It is worthy of note that the reticulocyte count is being accepted as the criterion of marrow response by the many workers who are using liver and liver extracts in the treatment of pernicious anemia.

Technic—Reticulocyte counts were made on fresh preparations. The technic used is that given by Robertson³. The blood is drawn into a pipet containing a dilute solution of brilliant cresyl blue in saline solution. After the pipet is shaken and allowed to stand for a few minutes, a drop of the blood is placed on a slide, quickly covered with a thin cover and sealed with petrolatum. The preparation is then examined with the oil immersion lens, and the reticulocyte count is expressed as the number present in 1,000 cells or in percentage.

In a series of papers,⁴ Downs and Eddy recorded the observations which led them to conclude that secretin is a stimulant of blood-forming

1 Krumbhaar, E. B. Reticulosis—Increased Percentage of Reticulated Erythrocytes in the Peripheral Blood, *J. Lab. & Clin. Med.* 8:11, 1922.

2 Key, J. A. Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, *Arch. Int. Med.* 28:511 (Nov.) 1921.

3 Robertson, O. H. The Effects of Experimental Anemia on Blood Production, *J. Exper. Med.* 26:221, 1917.

4 Downs, A. W., and Eddy, N. B. The Influence of Secretin on the Number of Erythrocytes in the Circulating Blood, *Am. J. Physiol.* 43:415, 1917; Secretin II Its Influence on the Number of White Corpuscles in the Circulating Blood, *ibid.* 45:294, 1918; Secretin III Its Mode of Action in Producing an Increase in the Number of Corpuscles in the Circulating Blood, *ibid.* 46:209, 1918.

tissue They observed a rapid increase in the number of red and white corpuscles in the peripheral blood of the rabbit after subcutaneous injections of 10 mg of secretin per kilogram of body weight The increase in red blood cells was about 20 per cent, and the height of the reaction occurred about an hour after the injection, the count then returning to normal The whole reaction was complete in approximately three hours They believed the rise in count to be due to the production of new blood cells

Fujimoto ⁵ later checked these results After the injection of secretin, he recorded a minimum rise of 5 per cent and a maximum rise of 64 per cent, the average being 25.75 per cent The increase in white

TABLE 3—*Author's Data on the Stimulating Effect of Secretin on the Blood*

Experiment Number	Initial Count	Maximum Count	Gain
21	6,280,000	6,900,000	620,000
22	5,120,000	6,920,000	1,800,000
23	5,610,000	7,160,444	1,550,000
24	6,400,000	6,920,000	520,000
25	5,510,000	6,160,000	650,000
26	6,020,000	6,510,000	490,000
27	4,390,000	6,430,000	2,040,000
28	5,940,000	6,170,000	230,000
29	5,270,000	5,110,000	160,000
30	4,930,000	5,060,000	130,000
31	3,370,000	3,630,000	260,000
32	4,030,000	4,340,000	310,000
33	4,660,000	5,430,000	770,000
34	5,030,000	5,690,000	660,000
35	7,130,000	7,390,000	260,000
36	1,510,000	4,640,000	3,130,000
37	4,500,000	5,220,000	720,000
38	4,650,000	4,920,000	270,000
39	4,500,000	5,110,000	610,000
40	4,980,000	5,230,000	250,000
41	4,800,000	4,970,000	170,000
42	4,850,000	4,910,000	60,000
Average	5,179,090	5,776,360	597,270
Average gain	11.1%		

cells varied from 3 to 96 per cent, the average being 34.75 per cent My data on similar experiments are given in table 3 The experiments were included whether there was marked or little response

Downs and Eddy's observations on the increase in number of corpuscles in the peripheral blood of the rabbit following the injection of secretin are corroborated Their conclusion, however, that the rise is due to the production of new blood cells is surprising in view of many well known facts concerning regeneration

There is no clinical or experimental evidence which would lead one to believe that an increase of a million or more cells per cubic millimeter of peripheral blood, taking place in about an hour and then returning

⁵ Fujimoto, B The Influence of Secretin on the Number of Red and White Corpuscles and the Ferments and Sugar Content of the Blood, *Am J Physiol* 47: 342, 1918

promptly to normal, could possibly be due to regeneration of new cells by the blood-forming tissues. All available evidence indicates that any rise in blood counts due to regeneration of new cells is slow, and, moreover, is not followed promptly by a return to the former level.

Lamson⁶ warned against regarding rapid changes in blood counts as due to the production of new cells. He said, "The fact that an increase of one million or more in the number of erythrocytes per cubic millimeter of blood takes place in from five to ten minutes, disappears in about an hour and may be repeated many times a day, is against the production of new cells, a decreased destruction or division of erythrocytes."

Scott⁷ emphasized the changes in concentration of the blood due to fluid exchange between the blood and tissue spaces.

Downs and Eddy's data show that by using intravenous injections they obtained increases as high as 40 per cent in as short a time as thirty-one minutes.

Hammett and Nowrey,⁸ working on the erythropoietic activity of germanium dioxide, called attention to the fact that the rise in red count which they used as a criterion of regeneration is not a transient reaction, but one which persists from eleven days to five weeks. This rise, moreover, is accompanied by other acceptable signs of regeneration, namely, "many polychromatic staining cells or young red cells."

Minot and Sampson⁹ published a work which contains valuable criticism of unwarranted deductions drawn from increased red counts by workers experimenting with hematopoietic stimulants. They pointed out that "merely an increase in the number of red cells in the circulation is ordinarily no indication of increased blood formation." Again, "Many of the red cell rises reported were moderate and transient and do not appear to have been controlled by a sufficient number of observations prior to administration."

6 Lamson, P. D. The Part Played by the Liver in the Blood Volume and Red Corpuscles Concentration in Acute Physiological Conditions, *J. Pharmacol. & Exper. Therap.* **16** 125, 1920.

7 Scott, F. H. Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces. I. Blood Pressure, *Am. J. Physiol.* **44** 298, 1917. Scott, F. H., Herrmann, E. T., and Snell, A. M. Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces. II. Muscular Activity, *Am. J. Physiol.* **44** 313, 1917.

8 Hammett, F. S., and Nowrey, J. E. The Erythropoietic Action of Germanium Dioxide. II. The Source of the Erythrocythemia Produced by Germanium Dioxide in the Albino Rat, *J. Exper. Med.* **35** 507, 1922.

9 Minot, G. R., and Sampson, J. J. Germanium Dioxide as a Remedy for Anemia, *Boston M. & S. J.* **189** 629, 1923.

Braun,¹⁰ working on blood destruction, made the following statement "But, as is well known, stimulation of marrow, even after considerable blood losses by hemorrhage, is not effective at once. Only after several days does the replacement of the lost corpuscles go on actively."

The work of Whipple, Robscheit and Hooper,¹¹ who studied the effect of various procedures on regeneration after hemorrhage, emphasizes the fact again that even under the best conditions the delivery of new cells to the circulation is a slow, gradual process. "Anemia is produced by bleeding one fourth of the measured blood volume on each of two successive days. This anemia will be completely repaired within three to four weeks if the dog is given a liberal diet of meat or beef heart."

Table 4 is taken from Bunting's work.¹² This shows the length of time required to regenerate about 1,000,000 new cells.

TABLE 4—*Results of Bunting's Experimental Work*

Date	Red Blood Cells	White Blood Cells	Experimental Procedure
4/27	5,416,000	14,750	Bled 30 cc from the vein of the ear
4/28	4,736,000	12,250	
29	4,904,000	17,250	
5/1	4,760,000	19,000	
5	5,363,000	9,125	
7	5,752,000	13,000	

Table 1 gives some data I obtained by the production in rabbits of various degrees of hemorrhage.

It is obvious that such rapid and transient rises in count as were observed by Downs and Eddy must be explained on some basis other than the production of new blood cells. One has only to consider the well known facts concerning the so-called solutions of secretin used to be convinced that the rises they observed were due to a concentration of the blood, and, furthermore, that such concentration was due not to the secretin contained in the solution, but to some of the many other substances inevitably present in such a tissue extract.

The tissue extract containing secretin is prepared as follows:

The upper part of the small intestine of the dog is washed, the mucous membrane is removed and ground up with sand. Fifty cc of 0.5 per cent hydrochloric acid is then added, after standing for two hours, the mixture is boiled actively

10 Braun, G. O. Blood Destruction During Exercise. II. Demonstration of the Blood Destruction in Animals Exercised After Prolonged Confinement, *J. Exper. Med.* **37** 113, 1923.

11 Whipple, G. H., Robscheit, F. S., and Hooper, C. W. Blood Regeneration in Simple Anemia. IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets, *Am. J. Physiol.* **53** 236, 1920.

12 Bunting, C. H. Experimental Anemias in the Rabbit, *J. Exper. Med.* **8** 625, 1906.

After it has been neutralized with sodium hydroxide and reacidified with acetic acid, it is strained through muslin and filtered. The resulting fluid is usually described as yellowish or greenish yellow and slightly opalescent.

Carlson, Lebensohn and Pearlman¹³ stated "In a maceration of duodenojejunal mucosa such as we have in secretin, the known substances are proteoses and peptones, acid amines, bile salts, beta-imidazole-ethylamine (histamine), choline, gelatin and inorganic salts."

Early in the experimental work with rabbits it was noted that there was a reaction which varied considerably with different animals and different doses. At times the animals appeared dyspneic, at times there was uneasiness which passed off and might even be followed by apathy, and occasionally salivation was noted.

Dogs were used in order to check the strength of the secretin. A cannula was placed in the pancreatic duct, and the drops of pancreatic juice were recorded by an electric drop recorder. Tracings of the blood pressure were taken simultaneously. The secretin solutions were given intravenously. Doses of sufficient size to stimulate the pancreas to any extent had a marked lowering effect on the blood pressure. Immediately following injection, there was unusually violent peristalsis and frequently breathing was rapid for a time. If more than 10 cc of the solution was injected quickly, especially if it was the first injection, the animals frequently died at once. Death was apparently due to cardiac failure. When the thorax was opened and the heart was examined, the ventricles were found to be in a state of violent fibrillation, which at times also involved the auricles.

Even these simple observations serve to show that one is dealing with some potent substance or substances. One quickly surmises that the hormone secretin is not responsible for these unusual physiologic effects. In fact, it is a simple matter to prove this point. If 25 cc of 5 per cent hydrochloric acid is injected into the duodenum, a comparable flow of pancreatic juice is obtained without the appearance of any of the phenomena mentioned.

It is probable that much more of the hormone secretin is liberated in the ordinary process of digestion than was administered by Downs and Eddy. Yet there is no reason to believe that the blood-forming tissues are stimulated to such an extent that the red count rises 20 per cent owing to the secretin liberated during digestion. Furthermore, Matsuo¹⁴ stated that "secretin administered subcutaneously, even in large quantities, is practically without effect." Carlson, Lebensohn and Pearlman¹³ stated that the hormone must be given intravenously to be

13 Carlson, A. J., Lebensohn, J. E., and Pearlman, S. J. Has Secretin a Therapeutic Value? *J. A. M. A.* 66:178 (Jan 15) 1916.

14 Matsuo, I. On the Secretion of Pancreatic Juice, *J. Physiol.* 45:447, 1913.

effective One can only conclude that the hormone, secretin, contained in the tissue extract used subcutaneously, did not play any part in the changes noted by Downs and Eddy

It is necessary at this point to consider the facts known concerning the physiologic effects of the tissue extract containing secretin in order to explain the nature of the increased counts observed by Downs and Eddy In the foregoing it was stated that such an extract contains proteoses, peptones, acid amines, bile salts, histamine, choline, gelatin and inorganic salts

Histamine was studied by Dale and Laidlaw¹⁵ in 1910 They made the following statement

Mention may be made at this point of the fact that preparations such as Witte's peptone and various organ extracts, resemble beta-aminazolyethylamine (histamine) in their action on the uterus as well as in other respects Figure 18 shows the effect on the isolated uterus of a virgin guinea-pig of adding to the bath 0.1 Gm of Witte's peptone dissolved in warm Ringer's solution The effect is indistinguishable from that of 0.1 mg of aminazolyethylamine Five-tenths cc of an extract of intestinal mucosa (containing also secretin) had a precisely similar effect

└

Barger and Dale¹⁶ reported the isolation of histamine from intestinal mucosa in an article entitled, "Beta-aminazolyethylamine, A Depressor Constituent of Intestinal Mucosa" They also noted that histamine increased the flow of lymph from the thoracic duct

It has been noted by others that tissue extracts (containing also secretin) cause increased flow of lymph from the thoracic duct Mendel and Thacher¹⁷ found that "the injection thus gave rise to an increased flow of lymph somewhat richer in solids—a feature characteristic of the action of certain lymphagogues"

Bainbridge¹⁸ also reported the increase in flow of lymph but was inclined to believe that it was due to the activity of the pancreas and, therefore, to secretin itself rather than to contaminating substances He stated, however, that ileum extract (which presumably does not contain secretin) also causes the increased flow if the portal lymphatics are not ligated In a later work¹⁹ on the flow of lymph observed in dogs post mortem, the same author stated, "The postmortem lymph

15 Dale, H. H., and Laidlaw, P. P. The Physiological Action of β -Aminazolyethylamine, *J. Physiol.* **41** 318, 1910

16 Barger, G., and Dale, H. H. β -Aminazolyethylamine, a Depressor Constituent of Intestinal Mucosa, *J. Physiol.* **41** 499, 1911

17 Mendel, L. B., and Thacher, H. C. On Secretin and Lymph Flow, *Am. J. Physiol.* **9** 16, 1903

18 Bainbridge, F. A. The Lymph Flow from the Pancreas, *Brit. M. J.* **2** 1742, 1904

19 Bainbridge, F. A. The Postmortem Lymph Flow, *J. Physiol.* **34** 275, 1906

flow after the injection of peptone is due either to filtration through abnormally permeable capillaries or to increased metabolism in the liver, the former view being the more probable "

Underhill and Ringer ²⁰ stated

It has long been known that the intravenous injection of "Witte Pepton" induces low blood pressure and a shock-like condition, which are accompanied by changes in the blood coagulation and an increased flow of lymph

It may be assumed that the direct cause of the blood concentration is the exit of fluid from the capillaries into the surrounding tissues which would account probably for the accelerated lymph flow

Dale and his collaborators have shown that with histamine there is a capillary damage due to the drug and the fall of pressure due to histamine is without effect per se

It is probable that peptone in itself changes the permeability of the capillaries in a manner analogous to that of histamine

The data of these authors show that with both histamine and peptone there is considerable concentration of the blood which varies in degree and time relations with the dose used and the rapidity of injection With peptone alone, the hemoglobin content may rise nearly 40 per cent The usual rise was between 20 and 30 per cent The injection of 0.5 Gm per kilogram of deuteroproteoses caused a similar concentration Histamine, likewise, causes a concentration which reaches a maximum more quickly and returns to normal more quickly

The same authors, in another article,²¹ reported their observations on "Vaughn's crude soluble poison" They found that it concentrated the blood in a manner somewhat similar to histamine They noted the striking resemblances between the physiologic actions produced by this substance or substances and those produced by histamine

Table 2 shows the results of the injection of an ordinary secretin solution intravenously into a dog

The foregoing statements will serve to call attention to the marked similarity in the physiologic reaction caused by such substances as histamine, peptone and proteoses and such a tissue extract as the so-called secretin, which is a mixture of all these and more The common response to such substances is a concentration of the blood Usually, an increased flow of lymph is also noted The consensus of opinion indicates that a change in capillary permeability is the essential factor in this reaction

One may summarize at this point by stating that the rapid and transient rise in blood count which Downs and Eddy observed to

20 Underhill, F. P., and Ringer, M. Studies on the Physiological Action of Some Protein Derivatives. V. The Relation of Blood Concentration to Peptone Shock, *J. Pharmacol. & Exper. Therap.* **19** 163, 1922

21 Underhill, F. P., and Ringer, M. Studies on the Physiological Action of Some Protein Derivatives. VI. The Influence on Blood Concentration of Vaughn's Crude Soluble Poison, *J. Pharmacol. & Exper. Therap.* **19** 179, 1922

follow injection (subcutaneous) of secretin is not characteristic of regeneration but is of the type known to occur after the administration of such substances as histamine, peptones and proteoses. The solutions used by Downs and Eddy are known to contain these and other substances. As the hormone secretin is not effective when given subcutaneously, one must assume that the concentration observed was caused by one or more of the other substances.

Thus far, attention has been confined to the first two papers by Downs and Eddy.²² Evidence has been advanced in support of two points: (1) that rapid and transient rises in blood count are not

TABLE 5—*Results of Downs and Eddy's Experiments on Rabbits Which Received Secretin and Control Rabbits*

"Secretin" Rabbits										
Num-ber	Blood Cells	Initial Count	First Week Average	Second Week Average	Third Week Average	Fourth Week Average	Fifth Week Average	Sixth Week Average	Seventh Week Average	Eighth Week Average
1	White	9,300	17,183	22,166	22,266	25 833	29,300	16,250	17,400	13,100
	Red	6,608,000	5,929,000	4,703,000	6,150,000	5,178,000	6,858,000	6,300,000	6,914,000	7,562,000
2	White	10,400	12,866	12,916	26,133	20,333	13,000	14 200	16,950	14,000
	Red	4,432,000	4,941,000	5,208,000	6,150,000	5,042 000	6,715,000	6,336,000	7,196,000	7,332,000
*	White	9,850	15,024	17,541	24,199	22,933	21,150	15,125	17,150	13,550
	Red	5,520,000	5,435,000	4,955,500	6,150,000	5,110,000	6,786,500	6,318,000	7,070,000	7,447,000
†	White	100 00	152 52	178 08	246 69	232 82	214 63	153 55	174 03	137 53
	Red	100 00	93 46	89 77	111 41	92 57	122 94	114 45	128 07	134 90
Control Rabbits										
3	White	7,100	7,833	7,166	11,800	7,833	7,600	6,800	9,000	8,533
	Red	6,272,000	5,536,000	5,784,000	6,121,000	5,386 000	6,336,000	6,574,000	6,616,000	7,250,000
4	White	9,800	9,166	6,916	9,100	9,600	10,100	11,250	12,600	10,433
	Red	6,176,000	6,081,000	6,194,000	6,253,000	6,377,000	7,530,000	6,856,000	6,481,000	7,244,000
*	White	8,450	8,499	7,041	10,450	8,716	8,850	9,025	10,800	9,483
	Red	6,224,000	5,808,500	5,989,000	6,187,000	5,886,500	6,933,000	6,715,000	6,548,500	7,247,000
†	White	100 00	100 57	83 31	123 66	103 14	104 73	106 80	127 69	112 22
	Red	100 00	93 35	96 25	99 44	91 60	111 39	107 89	105 21	116 43

* Averages

† Percentage relations

characteristic of changes due to production of new cells, (2) that the solutions used contained substances (other than the hormone secretin) which are known to cause temporary concentrations of the blood resulting in rapid and transient rises in count such as Downs and Eddy observed.

Their third paper²³ presents data obtained from an experiment planned to explain the mode of action of secretin.

Four rabbits were used. Two were given forty doses of secretin, and the controls were given saline solution. The experiment extended over eight weeks, the observations being made several times each week. The data are given in table 5.

22 Downs and Eddy (footnote 4, first and second references)

23 Downs and Eddy (footnote 4, third reference)

COMPARISON OF RESULTS

I repeated the experiment with twice as many animals. The following differences in technic should be mentioned. The animals in my "secretin" group received thirty-seven doses of secretin, while those of Downs and Eddy received forty doses. Fresh solutions were used

TABLE 6—*Results of Author's Experiments on Rabbits Which Received Secretin and Control Rabbits*

		"Secretin" Rabbits							
Num-Blood	Initial	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
ber Cells	Count	Week	Week	Week	Week	Week	Week	Week	Week
		Average	Average	Average	Average	Average	Average	Average	Average
29 Retieu-		16	25	30	41	60	60	37	37
loeytes			10,400	12,400	10,900	10,250	16,300	13,350	10,450
White	6,143,000	6,430,000	6,850,000	5,580,000	5,070,000	5,430,000	5,810,000	6,160,000	6,910,000
Red									
33 Retieu-		11	15	44	43	31	40	47	26
loeytes			12,200	18,500	14,700	13,350	13,450	22,550	16,500
White	5,675,000	5,710,000	6,070,000	4,840,000	6,160,000	5,840,000	5,790,000	7,340,000	7,460,000
Red									
34 Retieu-		6	11	34	45	62	45	39	47
loeytes			11,200	12,700	17,650	12,200	14,500	15,900	13,050
White	5,203,000	5,100,000	5,330,000	4,910,000	5,560,000	4,770,000	5,110,000	5,690,000	5,550,000
Red									
44 Retieu-		12	29	43	37	48	60	58	23
loeytes			11,630	11,700	11,950	18,080	13,100	13,150	13,150
White	5,220,000	5,350,000	4,090,000	4,879,000	4,900,000	5,270,000	4,550,000	5,650,000	5,400,000
Red									
* Retieu-		11 25	20 00	37 75	41 50	50 25	51 25	45 25	34 50
loeytes			11,375	13,825	13,800	12,200	14,337	16,237	13,287
White	5,560,500	5,647,000	5,595,000	5,050,000	5,422,500	5,327,000	5,315,000	6,210,000	6,330,000
Red									

Final count 113.8% of the initial count

		Control Rabbits							
Num-Blood	Initial	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
ber Cells	Count	Week	Week	Week	Week	Week	Week	Week	Week
		Average	Average	Average	Average	Average	Average	Average	Average
23 Retieu-			18	42	17	23	51	63	23
loeytes			17,000	12,200	21,500	10,900	11,550	9,000	9,150
White	5,400,000	5,700,000	4,360,000	5,100,000	6,530,000	5,520,000	4,960,000	6,130,000	6,240,000
Red									
28 Retieu-		34	18	50	25	25	38	62	38
loeytes			14,250	16,400	17,700	9,400	20,250	7,650	11,500
White	6,236,000	6,260,000	6,230,000	5,400,000	5,550,000	5,900,000	5,780,000	7,060,000	6,740,000
Red									
38 Retieu-		12	4	27	17	22	26	46	18
loeytes			28,800	25,800	27,050	22,050	35,300	22,000	16,700
White	6,693,000	7,470,000	6,390,000	6,500,000	6,550,000	6,970,000	7,430,000	7,990,000	8,080,000
Red									
40 Retieu-		21	7	34	25	31	54	48	49
loeytes			10,900	12,050	12,050	11,000	18,450	8,900	14,900
White	5,433,000	5,660,000	5,030,000	4,230,000	4,110,000	4,480,000	4,550,000	5,260,000	5,670,000
Red									
* Retieu-		22 30	11 75	33 25	21 00	25 25	42 25	54 75	33 25
loeytes			17,737	16,608	18,100	17,237	18,412	15,800	14,375
White	5,040,500	6,272,500	5,502,500	5,320,000	5,635,000	5,717,500	5,630,000	6,610,000	6,682,500
Red									

* Averages

The controls were injected with saline solution thirty-four times. The data are presented in table 6.

Downs and Eddy's "secretin" group finished the experiment with a red count which was 134.9 per cent of the initial count, the controls finished at 116.43 per cent. My "secretin" group finished at 113.8 per cent, while the control count was 112.5 per cent. Downs and Eddy felt

justified in assuming that the experimental animals showed a marked gain over the controls. Working with twice as many animals, I found the two groups as close together as could be expected, when a small number of animals is used.

So much importance is attached to the difference between Downs and Eddy's "secretin" and control groups that a careful analysis of the data seems necessary.

In comparing the percentages of gain in red blood cells it should be noted that the absolute difference between the two groups at the end of the experiment was only 203,000. The gain when expressed in percentage of the initial count seems to indicate a greater difference (secretin, 134.9 per cent—control, 116.43 per cent). This greater difference in the percentage of the initial count is due more to the lower count in the "secretin" group at the start of the experiment than to the relatively slight difference at the end. This may be illustrated by considering what the result would be in the case of rabbit 1 alone. The final count in this case would be 114.4 per cent of the initial count. This is less than the control gain. Therefore, the whole difference between the two groups rests on the fact that rabbit 2 had a temporary low count at the beginning of the experiment.

Any animal started at a count between 4,000,000 and 5,000,000 must show a gain when expressed in percentage of the initial count, as that is the low point in the animal's normal cycle. Nor is there anything unusual in such a count, as is evidenced by the fact that five of the eight animals used by me had counts between 4,000,000 and 5,000,000 some time during the eight weeks. As a matter of fact, it is obvious from both sets of data that, in general, any rabbit's count runs more or less in cycles varying from somewhat over 4,000,000 to somewhat over 7,000,000. For this reason any percentage of gain based on an initial count is so difficult of interpretation as to render its value doubtful.

A much better way of interpreting such data is to average the nine counts given for each animal. When this is done, one arrives at the following result (table 5).

"Secretin" Rabbits

Rabbit 1—Average of all counts	6,248,000
Rabbit 2—Average of all counts	5,928,000
Average for the group	6,088,000

Control Rabbits

Rabbit 3—Average of all counts	6,208,300
Rabbit 4—Average of all counts	6,576,800
Average for the group	6,392,550

This tabulation shows that the control group had a higher average than the "secretin" group, the difference being 304,550.

Similar data on my eight weeks' experiment are as follows (table 6)

"Secretin" Rabbits

Rabbit 29—Average of all counts	6,042,500
Rabbit 33—Average of all counts	6,098,300
Rabbit 34—Average of all counts	5,247,000
Rabbit 44—Average of all counts	5,034,300
Average for the group	5,605,525

Control Rabbits

Rabbit 23—Average of all counts	5,548,800
Rabbit 28—Average of all counts	6,128,400
Rabbit 38—Average of all counts	7,119,200
Rabbit 40—Average of all counts	4,935,800
Average for the group	5,933,050

The control group had a higher average, the difference being 327,525. This compares well with the difference between the two groups of Downs and Eddy (304,550).

Both sets of data show that the difference between the experimental and control groups is in favor of the control group.

The reticulocyte count varied from week to week, but when an average of the whole period is taken, the values for experimental and control groups correspond well, being 3.44 and 3.06 per cent, respectively. The experimental group shows the higher value, as would be expected from its slightly lower count.

COMMENT

The object of this paper is not to present a complete consideration of either regeneration or secretin, but to call attention to some well established facts concerning both, with which the conclusion that secretin is a stimulant of blood-forming tissue cannot be reconciled.

The facts on which the conclusion was based have been reviewed. In the first place, the sudden rise in red count observed (after the injection of the tissue extract), which returned promptly to normal, should not have been interpreted as suggestive of a regenerative phenomenon. The literature is replete with warnings on the point. Secondly, the data obtained in the long experiment (eight weeks), when interpreted in the light of knowledge concerning the normal cyclic fluctuation in the rabbit, do not furnish any evidence to support the contention that the experimental group showed more gain than the controls.

It would scarcely be logical to suppose that the small amount of secretin injected could produce so marked an effect, considering the relatively large amounts normally liberated, and it has been pointed out that the hormone is effective only when given intravenously.

It was likewise pointed out that substances present in the tissue extract used have been known for some time to cause transient concentrations of the blood .

Before concluding that a rise in red cell count is due to regeneration, it is necessary to show that the well known histologic signs of regeneration are present

CONCLUSION

The rapid and transient rises in cell count reported to follow the subcutaneous injection of the tissue extract containing secretin are corroborated. The rises are not due to regeneration, but to a concentration of the blood which is a characteristic response to such extracts

A NEW CLINICAL TEST FOR TISSUE THIRST*

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AND

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Recent reports by Aldrich,¹ who made tests by intradermal injections of physiologic solution of sodium chloride, showed clearly that edema was due to an increased hydrophilic action of the tissue colloids and not simply to renal obstruction. With this point in view, the following method was devised to study the colloid affinities of the proteins in the blood.

EXPERIMENTAL WORK

The apparatus used was a glass tube with a bell-shaped end. The bell end was closed with a collodion membrane, and the tube was filled with serum with a fine bacteriologic pipet. The tube was so graduated that when filled to a certain point it would read in percentage of swelling of the original volume of serum, as is shown in the illustration.

The ends of these tubes were then immersed in hundredth-normal hydrochloric acid, and the percentage of swelling was noted.

Dialysis of the same serum against water, physiologic solution of sodium chloride and various strengths of hydrochloric acid soon showed us that hundredth-normal hydrochloric acid gave the greatest amount of swelling. It is also true that variations in the thickness of the membrane within rather a wide range did not give variations in the amount of the swelling.

A series of serums from normal dogs and from normal persons were tested, and the amount of swelling was slight (table 1). Most of them swell 1 or 2 per cent, and 8 or 9 per cent is the maximum. In this connection it is interesting to note that in the appended list of controls numbers 17 and 18 showed considerable swelling, and subsequent study of the patients revealed that renal disease was present.

In a large series of cases this dialysis test was applied to nephritic and edematous patients. There was invariably a marked swelling. This ranged from 15 to 50 per cent (the limit of reading). Table 2 shows that this increased hydrophilic power of the serums is present not only in nephritis and uremia but also in edema of cardiac origin. In two cases of obstructive anuria there was little swelling (table 2).

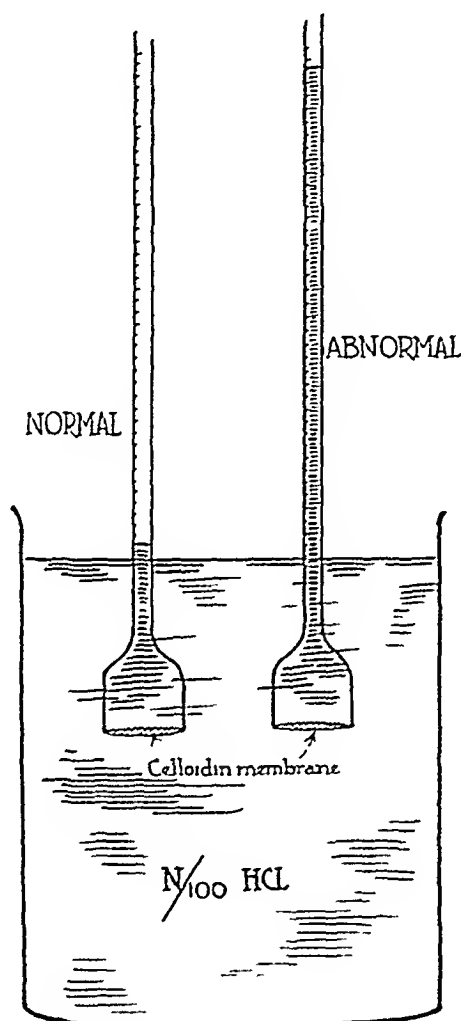
* From the Department of Surgery, University of Illinois College of Medicine.

1 Aldrich, C. A., and McClure, W. B. The Intradermal Salt Test, *J. A. M. A.* **82** 1425 (May 3) 1924. Aldrich, C. A. The Clinical Course of Generalized Edema, *J. A. M. A.* **84** 481 (Feb. 14) 1925.

COMMENT

The essential differences between uremic serums and normal serums consist in (1) greater acidity, (2) an increased amount of chlorides and (3) an increase in the amount of nonprotein nitrogen

With these points in view, the normal serums in both dogs and human beings were (1) acidulated by various means, (2) the sodium chloride content doubled and (3) large amounts of urea added. None of



The tubes are first sealed at the bell-shaped end with a celloidin membrane. They are then filled with serum up to the zero mark with a fine pipet and are finally immersed in hundredth-normal hydrochloric acid.

these procedures increased the hydrophilic power of normal serums to the slightest extent.

It is safe to assume, therefore, that this phenomenon resides in the character of the proteins in the serum. It is all the more striking when one considers that the uremic serums usually contain materially less protein than normal serums, and that in spite of this fact the protein which they do contain is able to absorb more water (table 3).

TABLE 1—*Controls*

Diagnosis	Per Cent Increase	Remarks
1 Normal	7	
2 Pneumonia	2	
3 Normal	6	
4 Normal	9	
5 Old fracture	3	
6 Normal	1	
7 Old fracture	15	
8 Old fracture	6	
9 Herniotomy, eight days	0	Local anesthesia
10 Carcinoma colon	3	
11 Fibroma	15	
12 Normal	3	
13 Old fracture	0.5	
14 Normal	4.0	
15 Appendectomy, four days after operation	3.0	
16 Normal	4.0	
17 Amputation, two months	10.0	Albuminuria, noted subsequently
18 Normal	16.5	Albumin and casts noted subsequently

TABLE 2—*Nephritis*

Diagnosis	Per Cent Increase
1 Edema, cardiac	18
2 Chronic nephritis	12
3 Dysentery and dehydration	14
4 Cardiac edema	8
5 Nephritis with edema	14
6 Nephritis with edema	10
7 Diabetic acidosis	11
8 Decompensation edema	14
9 Same case compensated	7
10 Postoperative vomiting	17
11 Severe hemorrhagic nephritis	28
12 Parenchymatous nephritis	36
13 Uremic coma	50+
14 Uremic coma	50+
15 Malignant hypertension	50+
16 Acute nephritis child	48
17 Two day anuria	50+
18 Beginning uremia twitching	40
19 Polycystic kidney anuria	50
20 Uremic hiccoughs	28
21 Prostatic obstruction anuria	16
22 Prostatic obstruction anuria	24

TABLE 3—*Relation of Protein Content to Swelling*

	Per Cent Swelling	Refractometer Reading
Normal human being (6 cases)	- 5.4	56.2
Human being with mild uremic condition	-22	50.4
Human being with severe uremic condition	-34	48.6
Human being with terminal uremia	-39	43.4
Child, anuric for eleven days	+61	40.0
Human being with cardiac edema	-18	49.8
Human being with renal edema	+33	48.4
Acute nephritis, increasing edema	-41	46.2

TABLE 4—*Relation of Protein Content to Swelling*

Source of Serum	Per Cent Swelling	Refractometer Reading
Dog 1, before injection	- 7	56.4
Dog 1, after injection (uremic)	-51	43.6
Dog 2, before injection	+ 4	53.7
Dog 2, after injection (uremic)	+33	42.0
Dog 3, before injection	+ 9	54.2
Dog 3, after injection (uremic)	-41	40.4

More striking still is the set of experiments on artificial uremia in dogs as previously reported by one² of us (table 4). In each of the three experiments, the protein content of the serum as measured by the refractometric reading fell about 25 per cent, but in spite of this fact it was able to absorb a great deal more water. Only two interpretations of these results are possible. In the serums exhibiting abnormal swelling, there is either (1) a foreign substance as protein, which enormously increases the osmotic pressure or is combined with a serum protein to do so, (2) or else the serum protein has undergone a profound change, perhaps a greater colloid dispersion, increasing its osmotic pressure abnormally. All present thought in nephritis points in this direction.

CONCLUSIONS

1 A simple method of measuring the degree of swelling of serum protein when dialyzed against hundredth-normal hydrochloric acid is described.

2 The swelling of normal serum is slight, that from nephritic and edematous cases very great.

3 This phenomenon is due either to the presence in the blood of some foreign protein or to some change in the colloid dispersion of normal blood proteins.

2 Andrews E. Experimental Uremia, *Arch Int Med* 40: 548 (Oct.) 1927.

DOES COMMERCIAL INSULIN CONTAIN WHAT HAS HITHERTO BEEN CALLED VITAMIN B?

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Studies on the occurrence of what has hitherto been called vitamin B have shown that this food factor is widely distributed in nature. It is found in most common foods of both plant and animal origin (Osborne and Mendel,¹ Sherman and Smith,² McCollum and Simmonds³ and Sherman⁴). Its distribution in animal tissues was investigated by Cooper,⁵ who used the pigeon method and found that the liver and cardiac muscle of the ox were good sources of the antineuritic, water-soluble vitamin. Similarly, Osborne and Mendel,⁵ using the growth of rats as the criterion for the presence of the water-soluble B-vitamin, reported that such tissues as the heart, liver, brain and kidney of the pig were rich in this food factor.

The presence of vitamin B in hormone preparations, however, is not so well known. A review of the literature revealed a paucity of such observations. Eddy⁷ demonstrated the presence of vitamin B in an extract made from the pancreases of sheep. From the results of feeding experiments with white rats, this investigator concluded that "the water-soluble portion of the alcoholic extract of pancreas contains a substance that is capable of inducing marked increase in growth." Likewise, Swoboda,⁸ using the yeast multiplication method, found that vitamin B was present in the pancreas and other glandular tissues.

During the course of an investigation concerning the physiology of vitamin B in the dog, it proved desirable to know whether commercial

¹ From the Laboratory of Physiological Chemistry, Yale University

^{*} The experimental data in this paper are taken from the dissertation submitted by Charles J Stucky in partial fulfillment of the requirement for the degree of Doctor of Philosophy, Yale University, 1927

1 Osborne, T B, and Mendel, L B J Biol Chem **32** 309, 1917

2 Sherman, H C, and Smith, S L The Vitamins, New York Chem Catalog Co, 1922

3 McCollum, E V, and Simmonds, N The Newer Knowledge of Nutrition, ed 3, New York, The Macmillan Company, 1925

4 Sherman, H C Chemistry of Food and Nutrition, ed 3, New York, The Macmillan Company, 1926

5 Cooper, E A J Hyg **12** 436, 1912, J Hyg **14** 12, 1914

6 Osborne, T B, and Mendel, L B J Biol Chem **32** 309, 1917, **34** 17 1918

7 Eddy, W H J Biol Chem **27** 113, 1916

8 Swoboda, F K J Biol Chem **44** 531, 1920

insulin contained appreciable quantities of this food factor. A comparison of the general properties of insulin (Macleod⁹) with those of vitamin B (Sherman⁴) makes it not at all unlikely that this accessory food substance is present in the hormone preparation. Study of the literature did not reveal that tests of this hormone for its vitamin B content had ever been made. Experiments with young rats were therefore performed. The curative type of procedure (in this case ability to restore growth) was employed, because it did not require the use of such large quantities of the insulin preparation.

EXPERIMENTAL DETAILS

The tests for vitamin B were made on a group of ten albino rats¹⁰ of the same litter, the individual animals weighing between 30 and 40 Gm at 21 days of age. They were placed in cylindrical, wire mesh cages with raised screen floors to prevent access to excreta (Steenbock, Sell and Nelson¹¹). Each rat was caged separately and handled according to the technic developed in this laboratory (Smith, Cowgill and Croll¹²).

Vitamin B Deficient Ration

	Per Cent
Meat residue *	18
Corn starch	50
"Crisco"	23
Cod liver oil	5
Salt mixture †	4

* This substance is practically free from vitamin B (Cowgill, G. R. *Am J Physiol* **79** 341, 1926). It may be obtained from the Valentine Meat Juice Company, Richmond, Va.

† The salt mixture described by Osborne and Mendel (*J Biol Chem* **32** 374, 1917) was employed.

The insulin used in this investigation was of standard purity. In preparing the hormone for the feeding experiments, 4,500 units of the aqueous solution (insulin, Lilly¹³) were mixed with 45 Gm of pure dextrin. This mixture was placed in an evaporating dish and heated gently over a hot plate for about four hours with occasional stirring, the temperature of the mixture being kept below 75 C, to avoid any possible destruction of vitamin B. At this temperature and for a considerable range above it, the vitamin has been shown to be stable (Sherman⁴). When thoroughly dry, the mixture was pulverized. The resultant product, a yellow-brown, sandy powder, was used for the vitamin B tests. Approximately 100 mg of this insulin-dextrin preparation was equivalent to 100 units of insulin.

9 Macleod, J. J. R. *Physiol Rev* **4** 21, 1924.

10 Obtained from the Albino Supply, Inc., Philadelphia.

11 Steenbock, H., Sell, M. T., and Nelson, E. M. *J Biol Chem* **55** 399, 1923.

12 Smith, A. H., Cowgill, G. R., and Croll, H. M. *J Biol Chem* **66** 15, 1925.

13 Obtained from the Eli Lilly and Company, Indianapolis.

In the feeding trials, the rats were fed on a ration deficient in vitamin B, having the composition shown in the table. The animals were fed the basal diet and water ad libitum. Dried brewery yeast,¹⁴ as a source of vitamin B, was fed apart from the ration at the rate of 100 mg per rat a day. All of the rats were placed on this dietary regime for about ten days, after which rats 1, 2 and 3, the controls, were continued on this ration while the remaining seven animals were deprived of the yeast supplement. When failure in growth or decline in body weight occurred, each rat was given a daily dosage of 100 mg of the insulin-dextrin preparation, fed separately from the rest of the ration, as a possible source of vitamin B. At the end of six days, the animals fed insulin had declined to such a great extent in body weight that 100 mg of yeast was substituted for the insulin preparation, this resulted in an immediate resumption of growth in all of the rats so fed. The chart demonstrates this clearly and shows the ineffectiveness of the insulin-dextrin preparation as a source of vitamin B.

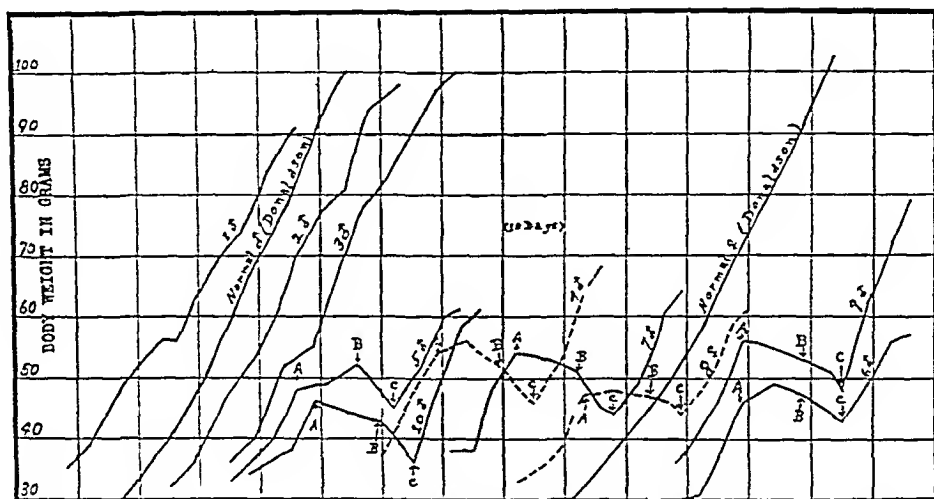


Chart showing that a young rat fed on a vitamin B deficient diet continued to decline in growth when receiving a daily supplement of 100 mg of an insulin-dextrin preparation as a possible source of vitamin B. The substitution of yeast for the insulin preparation was followed by an immediate resumption in growth. Each of the control animals (1, 2 and 3) received the same ration plus 100 mg of yeast daily from the beginning of the experiment. A represents the yeast withdrawn, B, the insulin added, C, the insulin replaced by yeast.

COMMENT

From the results of the experiments it is obvious that the insulin-dextrin preparation here used is markedly deficient in part at least, of the complex hitherto known as vitamin B.

Recently, papers have appeared bearing on the possible plural character of vitamin B, so called¹⁵. Although the experiments reported here were performed on rats, it is worth noting that a few attempts to cure

¹⁴ Obtained from the Northwestern Yeast Company, Chicago.

¹⁵ Sherman, H. C., and Axtmayer, J. H. A Quantitative Study of the Multiple Nature of Vitamin B. *J. Biol. Chem.* **75**: 227 (Oct.) 1927.

polyneuritic pigeons by large doses (from 50 to 100 units) of insulin per os were made in this laboratory¹⁶ and negative results were obtained. In these experiments the hormone was administered without further treatment, i.e., it was not evaporated down to dryness on dextin as in the experiments on rats. It would seem, therefore, that insulin is at least deficient in the antineuritic substance.

SUMMARY

A commercial insulin preparation was tested for its vitamin B content on a group of young albino rats. From the results of the feeding trials, it may be concluded that such material, when added to a diet deficient in vitamin B, will not support growth. Tests made with pigeons suggest that the antineuritic factor also is absent. Whether the heat-stable growth promoting factor, in what has hitherto been spoken of as vitamin B, is absent was not determined.

¹⁶ Experiments performed by Miss Margaret H. Jones, B. A., of the Graduate School, Yale University.

SKIN SENSITIVITY OF RHEUMATIC SUBJECTS TO STREPTOCOCCUS FILTRATES

ITS RELATIONSHIP TO RHEUMATIC FEVER ~

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The following work was carried out in order to determine whether one strain or a group of strains of streptococci exist which could be classed as rheumatic on the basis of the skin reactions in rheumatic subjects, and further to find if any immunologic characters were common to the varied types of streptococci which may be isolated in cases of rheumatic fever and chorea

Attempts made to isolate streptococci from the blood stream were largely unsuccessful. Thirty-three blood cultures were made from twenty-nine subjects, and the technic advocated by Clawson¹ was employed. All of the subjects were acutely sick with rheumatic manifestations, and the fever at the time of culture varied between 38.6 and 40 C (101.5 to 104 F). All except four had cardiac involvement. Eleven had pericarditis and ten had subcutaneous nodules. The cultures were kept from four to six weeks and examined semiweekly. Contamination with air organisms occurred in a few instances, otherwise all the blood cultures were sterile with one exception, a culture of the heart blood obtained immediately post mortem. A small gram-positive diplostreptococcus of the gamma type was obtained on this occasion, but did not grow on subsequent transplants. Cultures of spinal fluid in chorea and of joint fluid in acute articular rheumatism have been negative in every instance, although a small gram-positive diplostreptococcus was isolated on one occasion from a rheumatic pericardial effusion. It, too, did not grow on subsequent culture and its reaction on blood medium is unknown.

The "rheumatic" strains of streptococci finally employed were all obtained from the upper respiratory tract of children with rheumatic manifestations. Since streptococci may be obtained from a large proportion of cultures from the nasopharynx, and from the throat and tonsils, cultures were not considered suitable when the number of streptococci was very small. Thus of seventy-six cultures made, fifty-six strains of streptococci were considered sufficiently predominant to be suitable. Rather more than one half of the strains were isolated

¹ From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital

1. Clawson, B. J. J. Infec. Dis. 36:444, 1925

from the interior of the excised tonsils of convalescent rheumatic children. The remainder were obtained chiefly from the throats of subjects with acute rheumatic manifestations. A few were from sinus washings and ears where such foci seemed etiologic. In our series of cases, green streptococci could be isolated with equal ease during the acute and convalescent stage of the disease. Hemolytic strains were not commonly isolated during the period of acute sore throat, but were usually obtained during convalescence.

CLASSIFICATION OF ORGANISMS

The streptococci fell into two main classes: hemolytic and anhemolytic. The majority in the latter class were green, but five gray strains resembling, at least morphologically, the organism described by Small were included. The organisms were further classified according to their sugar fermentations. The sugars used were lactose, saccharose, inulin, salicin, mannite and raffinose. It was found that fourteen strains fermented lactose, saccharose and salicin and did not ferment mannite and raffinose. Three of these strains were green, the rest were hemolytic. The remaining strains showed considerable variation in their fermentation reactions. According to Andrewes' and Horder's² classification, most strains fell into the *salivarius* group, although three were classed as *fecalis* by their fermentation of mannite and a further two as *Streptococcus pyogenes*. This heterogeneity has been rather a general observation in previous studies of the organisms in the mouth in rheumatic fever.³ None resembled Small's⁴ strains in fermenting inulin. Similar fermentation tests made on a few of the control strains of streptococci, which will be described later, showed a predominating fermentation of lactose, salicin and saccharose, while one strain also fermented mannite. Thus the fermentation reactions did not distinguish the rheumatic strains from those of the control series. The organisms were also distinguished as scarlatinal and nonscarlatinal, both according to the skin reaction of the filtrate in groups of subjects with a positive reaction to the Dick test and those with a negative reaction, and by the ease with which intradermal injections of filtrates of streptococci belonging to the scarlatinal group were neutralized by either convalescent scarlet fever serum or commercial antitoxin when suitably diluted. None of the strains from rheumatic subjects fell typically into the class of scarlatinal strains. In nineteen filtrates from rheumatic sources, neutralization with scarlet fever serum occurred in five instances and

2 Andrewes, C. H., and Horder, T. *Lancet* 2 775, 1906.

3 Andrewes, C. H., Derick, C. L., and Swift, H. F. *J. Exper. Med.* 43 13, 1926.

4 Small, J. C. *Am. J. M. Sc.* 173 101, 1927.

was partial in four of these. The same filtrates, however, were rather easily neutralized by the serum of subjects giving negative reactions to this filtrate. Three of the control strains were neutralized completely by scarlet fever serum and showed intradermal reactions consistent with the Dick reaction of the subject.

These figures are lower than those of Williams,⁵ who obtained neutralization with scarlet fever antitoxin in 42.8 per cent of her filtrates of streptococci from excised tonsils.

The control group of streptococci consisted of twenty-four strains, ten hemolytic and twelve anhemolytic, isolated from the tonsils, throats and maxillary sinuses of nonrheumatic children.

EXPERIMENTAL METHOD

Technic of Growth—The material was seeded on blood agar plates, immediately after it was obtained. Aerobic and anaerobic cultures were examined after twenty-four hours, and when streptococci were present in abundance, flasks of veal infusion broth with 0.1 per cent dextrose and a p_H of 7.8 were inoculated and incubated for four days. It was found that usually anaerobic cultures were more abundant than aerobic, but none of the strains were strict anaerobes. The cultures were then centrifugalized, filtered through a Mandler filter and incubated overnight as a test of sterility.

Dilution of Toxin—The concentrated filtrate was diluted with normal salt solution until a 1:500 dilution was reached. At first dilutions of 1:100 and 1:250 were used, but it was felt that the uniform use of a rather high dilution would rule out those atypical reactions which occur with low dilutions in some persons, and which are due to sensitivity to some constituent of the filtrate other than the toxic principle. The amount injected was 0.1 cc., and the site used was the anterior aspect of the arm or forearm. The reactions were controlled by intradermal injections of filtrate, 1:500, heated for two hours at 100°C and of sterile medium similarly diluted.

Subjects Used—Two main groups of children were employed: a rheumatic group and a control group. The former consisted of seventy-five children between the ages of 5 and 15 years who were or had been suffering from chorea, rheumatic fever or rheumatic carditis. All were patients in the St. Louis Children's Hospital or the country department at Ridge Farm. They represented varying degrees of severity and were in different stages of sickness at the time examined. Many had been under continuous observation for over a year, and changes in their reaction to the various filtrates were noted and correlated with their physical condition. The control group consisted of 200 children of the same age group and from the same institution or from the Shriner's Hospital for Crippled Children. They did not have any history or physical signs of rheumatic stigmas. This control group was divisible according to the Dick reaction, 100 being positive to 2 standard skin test doses (STD) of Dick toxin and 100 negative to 50 STD of Dick toxin. This division was thought advisable, as it was considered that sensitivity of subjects to the Dick tests might run parallel to their sensitivity to other streptococcus filtrates. Hence, rheumatic subjects should not only be controlled by non-rheumatic subjects, but they should be compared with controls reacting similarly to the Dick test. The reactions were read at the end of twenty-four hours. Posi-

⁵ Williams, A. Am J Pub Health 15:129, 1925.

tive reactions measured 10 mm or more in diameter and usually resembled the Dick test. Frequently, the heated control showed a reaction as large as that produced by the unheated filtrate. This seemed to occur more frequently in some persons than in others, and in such instances neutralization tests with serum were not satisfactory.

RESULTS OF INTRADERMAL INJECTION OF FILTRATES FROM RHEUMATIC STRAINS

Forty-three filtrates, twenty-two from hemolytic and twenty-one from anhemolytic streptococci were tested on two main groups of rheumatic and nonrheumatic children. Each toxin was tested on at least thirty persons, ten of the rheumatic and twenty of the control series, the latter group being again divisible according to the Dick reaction. Ten of the filtrates as judged by this method were apparently nontoxic, this conclusion was reached only after at least thirty children had been

TABLE 1—*Results of Intradermal Injection of Streptococcic Filtrates from Rheumatic Sources*

	No. of Intra- dermal In- jections on Rheumatic Group	No. of Pos- itive Re- actions on Rheumatic Subjects	Percentage of Pos- itive Re- actions on Rheumatic Subjects	No. of Intra- dermal In- jections on Control Group	No. of Pos- itive Re- actions on Control Subjects	Percentage of Pos- itive Re- actions on Rheumatic Subjects
Hemolytic and anhe- molytic strains	487	111	22.8	829	106	12.70
Hemolytic strains only	311	96	30.86	481	98	20.36
Anhemolytic strains only	176	15	8.50	348	8	2.30

tested and had given negative reactions. Most of these nontoxic filtrates were obtained from anhemolytic strains, only one hemolytic organism failing to produce toxin.

The total number of intradermal injections made into all subjects with filtrates from rheumatic subjects was 1,316, of which 217 resulted in positive reactions. Thus, the percentage of positive reactions in the entire group of children under observation was 16.5. An analysis of the intradermal injections is given in table 1 to show the marked difference in the response of the rheumatic subject as compared with that of the control. It will be seen that the percentage of rheumatic children reacting positively is almost double that of the control series. This disparity is especially striking when the anhemolytic filtrates are studied separately, when the rheumatic subjects are shown to be about four times as susceptible as the controls. Birkhaug⁶ and Kaiser,⁷ using a similar technic and a filtrate from a "rheumatic" strain of streptococcus, demonstrated the increased skin sensitivity of rheumatic subjects.

6 Birkhaug, K. J. Infect. Dis. 40: 549, 1927.

7 Kaiser, A. D. J. Infect. Dis. 42: 25, 1928.

On the other hand, when one studies the sensitivity of this entire group of children to filtrates of streptococci obtained from nonrheumatic subjects, one is struck with the resemblances between the results in the two series. A total of 553 intradermal injections made in this group showed 16.66 per cent positive reactions—close to the 16.5 per cent of positive reactions obtained with the “rheumatic” filtrates. The resemblances hold when a more detailed study is made, as is outlined in table 2.

Here it will be seen that the percentages lie close to those given in table 1, and again that although a fairly wide difference exists in the sensitivity of the two groups to the hemolytic strains, this difference is greatly exaggerated when the anhemolytic group is studied. It is realized that the total number of positive reactions to the green and gray varieties of streptococci is small, but the difficulty of producing a

TABLE 2—*Results of Intradermal Injection of Streptococcic Filtrates from Sources Other than Rheumatic*

	No. of Intra- dermal In- jections on Rheumatic Group	No. of Pos- itive Re- actions on Rheumatic Subjects	Percentage of Pos- itive Re- actions on Rheumatic Subjects	No. of Intra- dermal In- jections on Control Group	No. of Pos- itive Re- actions on Control Subjects	Percentage of Pos- itive Re- actions on Rheumatic Subjects
Hemolytic and anhe- molytic strains	204	50	24.5	348	42	12.0
Hemolytic strains only	121	36	29.7	156	31	21.8
Anhemolytic strains only	83	14	16.8	192	8	4.2

toxic filtrate from anhemolytic strains of streptococci is well known. With other methods of culture and with the injection of lower dilutions of filtrate, more striking figures might be obtained, but on the other hand, the differences between the sensitivity of the rheumatic and control groups are sufficiently striking and it was felt advisable to keep the results as closely analogous as possible to those obtained with hemolytic strains. It was of interest to note that children belonging either to the rheumatic or to the control group who responded with positive reactions to one filtrate were likely to respond positively to several. The same held true for children with negative reactions. As it has been shown that many streptococci and also pneumococci have a nucleoprotein antigen in common to several strains,⁸ it seems possible that filtrates from such organisms may possess antigen characteristics in common and thus explain the tendency by which persons react to more than one filtrate.⁹

⁸ Avery, O. T., and Heidelberger, M. *J. Exper. Med.* **42**: 367, 1925.
Lancefield, R. C. *Proc. Soc. Exper. Biol. & Med.* **22**: 109, 1924-1925.

⁹ Zinsser, H., and Tamaya, T. *J. Exper. Med.* **42**: 311, 1925.

COMPARISON BETWEEN THE DICK TEST AND SENSITIVITY TO THE FILTRATES STUDIED

As was already explained, it was felt that the sensitivity of subjects to streptococcus filtrates might be to some extent parallel to their Dick reaction. If this were so, an error might be introduced, owing to the selection of two groups of unequal size in which the number of subjects in each group who gave positive reactions to the Dick test probably differed. The figures were, therefore, restudied from this new standpoint. By this comparison, an interesting difference was brought out in the sensitivity of rheumatic and control subjects. Consideration, first, of the filtrates from rheumatic sources shows (table 3) that the rheumatic subjects who gave a negative reaction to the Dick test were

TABLE 3—*Comparison Between Sensitivity to the Dick Toxin and to Streptococcic Filtrates from Rheumatic Sources*

	Rheumatic Subjects			Control Subjects		
	Total Intradermal Injections	+	Per Cent Positive	Total Intradermal Injections	+	Per Cent Positive
Dick positive	148	25	16.9	393	68	17.1
Dick negative	318	78	24.5	437	39	8.9

TABLE 4—*Comparison Between Sensitivity to the Dick Toxin and to Streptococcic Filtrates from Sources Other than Rheumatic*

	Rheumatic Subjects			Control Subjects		
	Total Intradermal Injections	+	Per Cent Positive	Total Intradermal Injections	+	Per Cent Positive
Dick positive	72	18	25.0	172	26	15.1
Dick negative	138	32	23.1	176	16	9.9

apparently considerably more susceptible to the filtrates than those in the group with the positive reaction. The control subjects, however, showed what one would have expected, namely, a greater percentage of positive reactions among the subjects positive to the Dick test. On the other hand, similar study of the control filtrates shows results which are much closer to those which were expected. The rheumatic subjects who are positive to the Dick test are slightly more sensitive than those who are negative. Of the control subjects, the relative sensitivity of the subjects positive to the Dick test and those negative to it is almost identical with that shown in table 3.

IS SENSITIVITY DEPENDENT ON THE TYPE OF RHEUMATIC MANIFESTATION OR ON THE STAGE OF THE DISEASE?

It was felt that if a positive reaction occurring in a rheumatic child was evidence of a rather specific sensitization, this sensitivity might vary

with the type of rheumatic manifestation present and also with the course of the disease. By watching a group of such children for some time, the reaction which took place to intradermal injections could be compared with the clinical observations. The results of this observation are shown in table 5, which illustrates two interesting points: first, the low percentage of positive reactions obtained in cases of acute carditis often accompanied by low grade chorea or joint pains, second, the high percentage of positive reactions obtained in the series of cases of acute rheumatic fever and acute chorea in which the changes in the heart were slight or could not be detected clinically. More light was shed on this difference by following the results of some of the intradermal injections over a considerable period of time and correlating changes in reaction with clinical changes in the patient. The tests were repeated after periods of from one to eighteen months, and when changes were observed, the intradermal injections were repeated many

TABLE 5—*Percentages of Positive Reactions Occurring in Various Forms of Rheumatism and Stages of the Disease*

Rheumatic Filtrates Used			
Type of Rheumatism Present at Time of Intradermal Injection	Total	Active	Clinically well or Inactive
Rheumatic fever	28.0	62.5 *	21.4
Chorea	25.6	34.6	22.5
Carditis, when acute frequently accompanied by chorea or rheumatic fever	20.5	10.5	21.97

*Series very small

times. In thirty-one instances a changed reaction was observed. Three of these occurred in the control group of children and in those three cases acute infection or any other factor could not be traced as a reason for the change. Among the patients in the rheumatic group, the changes fall into two main types and may be summarized as follows: subjects with chorea or rheumatic fever in whom an overwhelming cardiac infection is not present passed from a stage of positive to negative skin reactions. This was almost invariably true in the cases that were followed and in which the reaction was positive during the acute stage, and was seen in fourteen instances. In only five children in whom the intradermal injections were repeated during the clinical course of the disease was no appreciable change of the skin reaction observed. This change may be analyzed further according to the appearance of the positive reaction. In some cases, the reaction resembled a Dick reaction. The controls of filtrates heated at 100 C. for two hours were negative, and the skin reaction was rather readily neutralized. In contrast with this were a large number of indurated reactions when the toxic substance was heat stable and when neutralization could not be effected. These

reactions lasted longer and resembled somewhat a Schick reaction. It was found that the commonest reaction obtained during the acute phase was the flat positive, and that during early convalescence practically every child showed an indurated positive response. The same intradermal injections repeated when the children were clinically well usually gave negative reactions, although in five instances the reactions did not become negative during the period of observation. In one instance, after going through the positive and negative phase, the test again gave a positive reaction. Three persons watched for over a year developed positive skin reactions when previously they had given negative reactions. In one case a mild acute rheumatism followed the change, while another child remained well. The third instance occurred in a child who had had chorea one year previously and in whom an effort had been made to produce skin sensitivity by injecting filtrate obtained from the subject's own throat organisms. The acquisition of skin sensitivity was followed by a recurrence of chorea, but it is felt that other factors played a more important rôle. This phasic change of the skin reaction during rheumatic manifestations has an interesting parallel in the work of Dochez and Stevens¹⁰ on experimentally produced allergy.

An apparently different type of changed reactivity from that just described was seen in those patients who after showing a positive reaction developed a fulminating carditis with high temperature, pericarditis and pulmonary involvement. In five such instances, the positive test became negative, and in the only surviving patient a return to a positive reaction was observed as recovery occurred. The same phenomenon was observed a second time in the same patient during a subsequent recrudescence of rheumatic pleuritis. This altered reactivity may be explained on the basis of anergy as a Dick test was similarly diminished in those cases in which it had previously been positive. Anergy to tuberculin in rheumatic fever has been described in the literature.¹¹ Spontaneous loss of sensitivity to streptococcus filtrate occasionally occurs without obvious infection or operative procedure to explain the change.

NEUTRALIZATION OF INTRADERMAL INJECTIONS WITH SERUM OF SUBJECTS FROM WHOM STRAIN WAS OBTAINED

Samples of serum were obtained from most of the subjects during both the acute and the convalescent stage of the disease. This serum was mixed with the diluted filtrate of the organisms from the same subjects from whom the serum was obtained and injected intradermally.

10 Dochez, A. R., and Stevens, F. A. *J. Exper. Med.* **46**: 487, 1927.

11 Magni, Luciano. *Riv. di Clin. Pediat.* **25**: 27, 1927, abstr., *Am. J. Dis. Child.* **33**: 991 (June) 1927.

into persons with positive reactions. The filtrate was diluted so that 0.1 cc contained 4 STD. It was then mixed with double the volume of serum and incubated for one hour. It was thought that a difference in the neutralizing properties of the serum taken at different stages of the disease might be demonstrable. It was found, however, that neutralization was easily effected in the majority of cases and no difference could be demonstrated in the neutralizing power of acute or convalescent serum of the same subject. In four instances, neutralization did not occur, although the subjects from whom the organism and serum was obtained had negative skin reactions. Neutralization also occasionally occurred with the serum of subjects who gave positive reactions to intradermal injections of their own organisms. The serum of persons who gave negative reactions to the filtrates neutralized such filtrates rather readily on susceptible subjects. This observation is contrary to that of Mackenzie and Hanger,¹² but it is felt that as they injected much larger quantities of filtrate the reactions obtained were not entirely due to the neutralizable toxic substance.

ATTEMPT TO FIND CIRCULATING TOXIN IN THE BLOOD OF RHEUMATIC SUBJECTS

It was thought that if rheumatic fever depended, as scarlet fever apparently does, on the presence of a circulating toxic material, it would be possible to demonstrate this by injecting intradermally the serum of acutely sick children into rheumatic and nonrheumatic subjects. Twelve serums from acute cases with pericarditis, fever and rheumatic nodules were so tested on forty rheumatic and twenty control subjects. Positive intradermal responses measuring 10 mm or more did not occur, although 0.3 cc was injected each time. This does not rule out the presence of some toxic material in slight amounts, and it is possible that the serum was not taken from sufficiently early cases.

RESULTS OF INTRAMUSCULAR INJECTION OF TOXIC FILTRATE

A further attempt to trace a resemblance between the mechanism of rheumatic and scarlet fever was made by injecting increasing amounts (from 0.001 to 1 cc) of toxic filtrate into subjects convalescing from chorea. One such patient in whom skin sensitization to the filtrate was already present developed fever, general malaise and local inflammation at the site of injection, but increase or decrease of her symptoms did not occur. A normal subject whose skin was sensitive showed exactly the same symptoms. Of the other two subjects who were given injections of filtrate from organisms from their own throats, one became

¹² Mackenzie, G. M., and Hanger, F. M. *J. Immunol.* **13**: 50, 1927.

skin sensitive and subsequently developed chorea, and the other did not become sensitized or show any clinical change. It is felt that greater success might have been obtained if only subjects showing a positive skin test as evidence of the presence of an alleigizing focus had been employed.

A difference was not noted in the toxicity of filtrates from streptococci isolated during the acute and convalescent stages of the disease, and a difference apparently did not exist in the toxicity of the organisms whether they were obtained from cases of rheumatic fever or chorea. Although the figures in table 1 give the impression that the filtrates of the various strains had a uniform distribution of positive reactions, this was not the case. Several filtrates, especially of hemolytic strains, gave identical percentages of positive reactions in the rheumatic and control series, and in a few the controls seemed relatively more susceptible. However, in a large proportion of the hemolytic and in most of the green strains, the increased susceptibility of the rheumatic subject was marked.

THE DICK TEST IN RHEUMATIC FEVER

The Dick test was studied in seventy-seven rheumatic subjects. All were given injections of 2, 20 and 50 STD of standard Dick material. It was found that seventeen, or 22 per cent, gave positive reactions and that sixty, or 78 per cent, gave negative reactions to 2 STD. These observations may be contrasted with those of Cooke¹³ working with children of the same age group and in almost identical circumstances where 35.5 per cent were Dick positive. Zingher's¹⁴ figures, although from a different group of children, accord with those of Cooke. Occasional spontaneous change of a positive to a negative reaction is seen in nonrheumatic subjects. This was seen once in a rheumatic child after an attack of acute tonsillitis which had many of the characteristics of true scarlet fever. This was the only instance in which a marked change occurred, the child being positive to 2 STD before the injection, and negative to 50 STD subsequently. In seven of twenty-eight cases in which the Dick test was made both during the acute and convalescent phase, a rather consistent change was seen. The test, negative during the acute phase, became positive. This temporary negativity of the Dick test in acute diseases has been the observation of others, and is an interesting contrast to the behavior of other streptococcus filtrates during the acute and convalescent stages of rheumatism.

13 Cooke, J. V. *Scarlet Fever. II. The Development of Toxin Sensitivity of the Skin in Infants and Its Relation to the Presence of Antitoxins in the Blood*, *Am J Dis Child* **35** 762 (May) 1928.

14 Zingher, A., quoted by Park, W. H. *Scarlet Fever. Etiology, Prevention by Immunization, and Antitoxic Treatment*, *J A M A* **85** 180 (Oct 17) 1925.

COMMENT

A survey of the literature for the last thirty years on the etiology of rheumatic fever shows a gradually increasing belief in its streptococcic origin. Most workers have felt that the specific characters of the disease must be due to a specific etiology, and many so-called rheumatic organisms have been described. The possibility of a specific reaction of certain persons to a heterogenous group of bacteria was suggested by Menzer¹⁵ as early as 1902, but this lead has not been generally followed. The rare occurrence of streptococci in the blood and tissue fluids of rheumatic subjects and the inability to reproduce the disease by the most diverse methods of injecting streptococci leads one to believe that the disease is not produced by a blood stream infection. A heterogenous group of cocci may be etiologic, and in this connection Zinsser¹⁶ mentioned an interesting case in which two distinct strains of streptococci, one a typical viridans and the other belonging to the gamma group, were isolated in a case of rheumatic fever. Swift and his colleagues¹⁷ have also made this observation.

With the intradermal method of injection of the filtrable products of streptococcus, the rheumatic subject has been shown to be much more susceptible than the control to these filtrates as a group. This sensitivity, however, varies from the numerous positive reactions obtained when some filtrates are used to the slight sensitivity to others, including the Dick toxin. The validity of the skin test as a test of sensitivity may be questioned on theoretical grounds, but it is felt that sufficient analogy existed between rheumatism and tuberculosis to make the significance of the skin test possibly similar. The results obtained seem to have justified this assumption. It might be felt, too, that rheumatic subjects who are known to have frequent infections of the upper respiratory tract owe their skin sensitivity to these frequent infections and not to an underlying rheumatic condition. The evidence, however, suggests a closer relationship between positive reactions to intradermal injections and the rheumatic manifestations. Subjects who are suffering from acute diseases other than rheumatic conditions tend to give negative reactions during the acute stages of their illness and later, positive reactions, this has also been the experience of Mackenzie and Hanger¹². A similar phenomenon occurs with the

15 Menzer, A. Die Aetiologie des acuten Gelenkrheumatismus, Berlin 1902, *Ztschr f klin Med* **47** 109, 1902.

16 Zinsser, H. *Bull N Y Acad Med* **11** 351, 1928.

17 Swift H F, Derick, C L, and Hitchcock, C H. Bacterial Allergy to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, *J A M A* **90** 906 (March) 1928. Swift, H F, and Kinsella, R. Bacteriologic Studies in Rheumatic Fever, *Arch Int Med* **19** 381 (June) 1917.

Dick reaction Rheumatic children, on the other hand, show a positive intradermal reaction during the acute phase and tend to be negative during convalescence

Dochez and Stevens¹⁰ were able to watch the changing response to intradermal injections in rabbits immunized against an erysipelas strain of streptococcus They found that an early negative phase was succeeded by a positive skin reaction and that this phase in turn could be subdivided into a primary stage in which the reaction was neutralizable and in which a reaction did not occur when the filtrate was boiled and into a second stage in which the reaction was not neutralizable and in which the filtrate if heated gave rise to reactions as extensive as those produced previously The flat positive reaction followed by the induced positive reaction in acute and subacute rheumatism and chorea are striking analogies to those reactions which were described by Dochez in the early stages of immunization In his work and in the work presented in this paper, the positive response to intradermal injections was followed by a period of negativity Only one of the patients was followed sufficiently closely to show a late return to the positive reaction, although three further instances occurred in which, after a period of negativity, the reaction again became positive Although lacking completeness, these studies show the same trend as do those of Dochez in experimental allergy and thus link an allergy to streptococcus infections due to a wide variety of organisms with the picture of rheumatic fever In the small group of cases in which an overwhelming cardiac infection occurred, the skin tests became negative This was true for all the filtrate tests made on each subject and also for the Dick test The Dick test also tended to be less positive during acute rheumatic conditions than it was after convalescence In other words, the Dick test varied in rheumatic children as it does in other children during acute infections, while the behavior of streptococcus filtrates in fulminating carditis may be due to the same factors or may be explained by desensitization

The low percentage of positive Dick tests occurring in this rheumatic group in which one would rather imagine it to run parallel with the high percentage of positive reactions with other filtrates was, at first sight, surprising It was also difficult at first to conceive how one diverse group of streptococci could sensitize rheumatic children, while with other smaller equally diverse groups rheumatic subjects seemed as little or less susceptible than the controls A possible explanation for both these differences may be found in the varying ability which different strains of streptococci possess in stimulating antitoxin production. Infection with the scarlet fever strain or strains usually results in the production of circulating antitoxin and of considerable immunity to the disease This is not always demonstrable in other diseases of streptococcic origin in which the patient frequently remains susceptible

It is thought that the low incidence of positive Dick reactions compared with the high incidence of positive reactions to intradermal injections of filtrates of other strains of streptococci may be correlated with the varying ability of different strains of streptococci to produce a neutralizing antitoxin. According to this theory, one would suppose that rheumatic subjects were hypersensitive to all streptococci from an early age, and that this increased sensitivity was masked in the case of scarlatinal and some other strains by the production of circulating antitoxin. Thus, the group of children with the low percentage of positive Dick tests would be that group most frequently infected by streptococci in general, and would show a high percentage of positive skin reactions to those other strains. On the other hand, among the controls in whom less infection with organisms of the upper respiratory tract had occurred, sensitivity to one organism, e.g., the scarlet fever streptococcus, would be paralleled with sensitivity to others, and the infection would have been insufficient to mask sensitivity by the production of antitoxin.

The technic of neutralization of products of streptococci with supposedly immune serum is less satisfactory than neutralization of the Dick toxin. In most of the persons who gave negative reactions to the filtrates, antitoxin could be demonstrated in the blood, but neutralization tests with such serums were not invariably successful, that is, in one or sometimes two of a group of four subjects on whom neutralization tests were made, neutralization could not be accomplished. Such tests were least successful when made on subjects in the subacute stage of rheumatic fever and chorea who showed an induration in the skin test with sensitivity to the heated filtrate. Difficulty was not experienced in neutralizing those tests in which the positive reaction occurred only with the unheated filtrate and the reaction was not indurated. The ability to neutralize such intradermal tests was first pointed out by Dochez and Sherman¹⁸ and by Dochez and Stevens¹⁹ working with erysipelas and scarlet fever strains of streptococci. No differences could be shown in the antitoxin titer of the serums taken from rheumatic subjects at different stages of the disease, and it is conjectured that the response of the rheumatic person does not involve to any extent the mechanism of antitoxin production.

The percentage of positive reactors among the control series of nonrheumatic children seems significant. Several of them showed the raised positive reaction similar to that occurring in rheumatic subjects. None, however, had a history or physical signs of rheumatic infection. It is probable that some difference exists in the tissues of rheumatic

¹⁸ Dochez, A. R., and Sherman, L. *Proc Soc Exper Biol & Med* **22** 282, 1925

subjects which, with the acquired allergy to organisms common in the throat, determines the specific characters of rheumatic fever and chorea

It would be rash to assert, on the basis of these observations, that in suitable persons all strains of streptococci could cause rheumatic fever and chorea. What seems probable is that rheumatic fever is an allergic response to common streptococci and occurs in certain persons whose tissues for some reason respond differently. It is possible to demonstrate this hypersensitiveness by using the products of all types of streptococci for intradermal injections. The possibility of rheumatic fever being caused by a certain special group of streptococci is not ruled out, for in this case the positive skin reactions to other strains could be explained by the nonspecific response of the tissues to an antigenic fraction common to a large group of streptococci. One feels, however, that this would be unlikely because of the heterogeneous group of streptococci to be found in the tissues and throats of rheumatic subjects, and that at least the members of the wide anhemolytic group are most probably implicated.

SUMMARY

1 The streptococci of the upper respiratory tract of rheumatic children are identical culturally and immunologically with those from normal children

2 Persons suffering from rheumatic fever show marked sensitivity of the skin to filtrates from a wide group of those streptococci either from rheumatic or normal subjects

3 This sensitivity is most marked in the acute stages of rheumatic fever and chorea, especially when acute carditis is not present. It is least marked when the subjects are clinically well

4 In those cases in which the skin reactions are followed over a period of time, it is possible to divide the skin reactions into definite phases which are analogous to certain cases of experimental allergy

5 These observations indicate a definite relationship between rheumatic fever and streptococcal infections, but do not implicate any particular strain of organism. It is suggested that the rheumatic syndrome is an allergic response of certain predisposed persons to the common streptococci of the upper respiratory tract

Book Reviews

CONSTITUTIONAL INADEQUACIES AN INTRODUCTION TO THE STUDY OF ABNORMAL CONSTITUTIONS By NICOLA PENDE, M D, Professor of Clinical Medicine, Royal University of Genoa, Italy Translated by Sante Naccarati, M D, Sc D, Ph D, Associate Professor of Nervous and Mental Diseases, Post-Graduate Medical School of New York, New York City With a foreword by George Draper, M D, Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Chief of Constitution Clinic, Presbyterian Hospital, New York City Price, \$3 50 Pp 270, with index Philadelphia Lea & Febiger, 1928

Shaw has taken us "back to Methuselah", Pende takes us back to Hippocrates and Galen This interesting monograph is a presentation, in the language of twentieth century biology and medicine, of the ancient idea of preponderance of specific humors or elements giving rise to the individual characteristics of a person By constitution the author understands the hereditary potentialities of the individual protoplasm as modified by individual experience "Constitution is determined principally by the internal evolutionary destiny assigned to each individual at the moment of conception"

We have no quarrel with this definition except the phrase "at the moment of conception" Of course, it is clearly established that hereditary factors are present in the germ cells before the moment of conception Nothing is given to the germ cells in the way of evolutionary potentials at the moment of conception except that which results from an admixture of the two germ cells This conception of constitution is probably true, but is certainly not new

According to Dr Pende constitutional inadequacies are such defects or injuries, either originally hereditary potentialities or accidentally induced by environment, that prevent perfect internal coordination and perfect adjustment to the external environment Such constitutional inadequacies constitute or lead to disease

In the second chapter the author gives anthropometric measurements from which the attempt is made to predict the kind of constitutional inadequacies (diseases) that the person is apt to develop during the different stages of life Like other authors of this school, Dr Pende is strong on classification He analyzes, criticizes, rejects or adopts elements of classification by previous authors who have written on constitutional pathology or disease as the expression of defects in the constitution To what extent this type of work will advance medicine depends on the quantitative accuracy of the measurements or tests and on a number of persons included in the measurements At present the whole matter is essentially an interesting working hypothesis It has led to nothing definite in either therapy or prophylaxis

Unfortunately, the volume is marred by a great many ambiguities We are unable to state (not being familiar with the original Italian) whether these ambiguities are due to Dr Pende or to the translator, Dr Naccarati Possibly some of the ambiguities are inherent in the theory, but occasionally they seem to be due merely to the love on the part of the author or the translator of sonorous sounds For example "in the case of familial constitutional hypertonia that I have observed the habitus of the patients corresponded to the megalosplanchnic hyperpituitary, hypergenital and hyperadrenal constitution This accords well with the stimulatory action exerted upon the cardio-arterial muscular tonus by the genital, neurohypophysial and adrenal hormones, especially after puberty, and enables us to understand also how another constitutional anomaly coordinated with the preceding in these same individuals might be a vaso-motor nervous hyperexcitability, a tendency to angiospasm, a neuropathic diathesis, predominantly sympathicotonic since the aforesaid hormones stimulate the sympathetic tonus and excitability" (p 156)

The accounts of the natural history and probable phylogeny of the primates from lemurs to men, and the analysis of the skeletal remains of our human and prehuman ancestors, with its wealth of pictorial illustration, seem to be intended for general readers, but they will not find it easy. Fondness for sonorous polysyllables gives evidence of great erudition, but one wonders how far the lay readers will go into description of this sort. "In *hylobates* the brachiating type of locomotion has replaced the pronograde specialization of lower primates."

Interlarded with these chapters are technical neurologic descriptions which are beyond the grasp of any but expert neurologists and which even for these are tantalizing because of their incompleteness and in some places their inaccuracy. The obvious things are pointed out with tedious reiteration, but the details of interest to neurologists are notably lacking. This leaves one with a feeling of exasperation, for when one expects exact description and illustration, one finds too often only banalities. The method of preparation of the measurements, indexes and reconstructions of internal organs of the brain stem are not given with sufficient precision to enable the critical reader to evaluate them, or in some cases to understand them. Illustrations are given of reconstructions of the gray matter of the brain stem of eleven species of primates, including man. When the pictures of reconstructions of the human brain stem are compared with the drawings of Weed's carefully made model, they seem to have little resemblance. Why is this? The photographs of the gross specimens leave much to be desired, and the accompanying key drawings, which we should expect to supplement the photographs, are too sketchy to add anything of value.

There is undoubtedly much of interest in these volumes, but as one puts them back on the shelf it is with a feeling of disappointment that so large a labor and so good a manufactured product, on the publisher's part, should be so blemished by inaccuracies and deficiencies as to fall far short of what a scientific treatise should be.

LOW BLOOD PRESSURE ITS CAUSE AND SIGNIFICANCE By J F HALLS DALLY
Price, \$5 New York William Wood & Company, 1928

In recent years there has been a decided tendency toward interest in the subject of low blood pressure, perhaps because some of us are tired of the question of high blood pressure. The present book was written in the hope of presenting this subject from a broad biologic point of view. The general discussion of the physiologic significance of blood pressure is excellently given, then the author proceeds to the question of low arterial pressure, particularly in regard to its etiology. The standpoint is taken that patients with low arterial pressure may be considered as having a low vitality secondary to constitutional or to nutritional disorders or disturbances of the endocrine glands. It is assumed that a change occurs in the "acid-base tissue balance," so that these patients are much more likely to have a high ratio of alkali to acid in the urine. This biochemical change is given considerable emphasis without, however, a sufficient presentation of the actual facts underlying this supposed abnormality of metabolism. At any rate there is an excellent review of all the other views of the etiology of hypotension followed by a complete discussion of the multitude of conditions and diseases in which low blood pressure may be found.

The diagnosis and prognosis are intelligently discussed, and the chapter on the general management of low arterial pressure includes most of the measures which have been agreed on as beneficial for hyposthenic persons. In this chapter, however, one finds such suggestions as the subcutaneous injection of oxygen as a treatment. Organotherapy also is prescribed in a rather uncritical fashion, comprising extracts of thyroid, pituitary, suprarenal and gonadal glands either singly or combined. It is unfortunate that this last chapter contains a considerable amount of uncritical therapy.

On the whole, however, this book represents an excellent review with a thorough discussion of most of the significant literature on the subject of low blood pressure, and should be of value to all who are interested in this field of cardiovascular conditions.

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PRODUCTION OF RENAL INJURY IN THE WHITE RAT BY THE PROTEIN OF THE DIET

DEPENDENCE OF THE INJURY ON THE DURATION OF FEEDING,
AND ON THE AMOUNT AND KIND OF PROTEIN ¹

L H NEWBURGH, M D

AND

A C CURTIS, M D

ANN ARBOR, MICH

In 1919,¹ and again in 1923,² one of us (L H N) reported the production of structural damage to the kidneys of rabbits by feeding them diets which contained large amounts of several kinds of protein. These experiments were adversely criticized on four scores: 1 The frequent spontaneous occurrence of renal lesions in the rabbit made it difficult to prove that any given injury was caused by the experimental procedure. 2 The herbivorous rabbit, habituated to a dietary low in protein, was a poor test object if the results are to be transferred to man. 3 The diets were inadequate. 4 The lesions were due to the acidity of the urine.

In reply to these criticisms, we began to feed properly constituted diets containing varying amounts and kinds of protein to white rats. During the ensuing interval of four years, a number of investigators have described the state of the kidneys of white rats which have eaten high protein diets. Some of these observers have noted well established lesions, whereas others failed to find satisfactory evidence of disease. We believe that we are able to explain this disagreement in the light of our own results. We will accordingly report our experiments and then deal with the publication of other workers.

EXPERIMENTAL WORK

We have carried out our feeding experiments according to the well known plan devised by Ferry.³

¹ From the Department of Internal Medicine, Medical School, University of Michigan.

² The expenses of this investigation were defrayed in part by grants from Parke, Davis & Co, and from the Fellowship Corporation.

1 Newburgh, L H. Production of Bright's Disease Through Feeding High Protein Diets, *Arch Int Med* **24** 359 (Oct) 1919.

2 Newburgh, L H, and Clarkson, S. Renal Injury Produced in Rabbits by Diets Containing Meat, *Arch Int Med* **32** 850 (Dec) 1923.

3 Ferry, Edna L. *J Lab & Clin Med* **5** 735, 1920.

In order to supply adequate amounts of vitamins and salts, every rat, after being weaned, received daily 1 tablet containing 50 mg of yeast extract. The diet itself contained 3 per cent of a tested cod liver oil and 4.5 per cent of the salt mixture described by Osborne and Mendel, when the protein was casein. Somewhat smaller amounts of the salt mixture were used when beef muscle or liver was the source of protein, because these materials contain considerable quantities of the various salts. The remaining ingredients of the diets were lard, cornstarch and protein. As the percentage of protein increased, the cornstarch was correspondingly decreased and finally omitted. In the case of diets high in protein, the percentage of lard was also decreased.

Diets Containing Casein

(1) About 7% Protein		(2) About 10% Protein		(3) About 15% Protein	
	Gm		Gm		Gm
Casein	8.0	Casein	12.0	Casein	18.0
Lard	24.5	Lard	24.5	Lard	24.5
Corn starch	60.0	Corn starch	56.0	Corn starch	50.0
Salt mixture	4.5	Salt mixture	4.5	Salt mixture	4.5
Cod liver oil	3.0	Cod liver oil	3.0	Cod liver oil	3.0
	100.0		100.0		100.0
(4) About 20% Protein		(5) About 26% Protein		(6) About 32% Protein	
	Gm		Gm		Gm
Casein	25.0	Casein	32.0	Casein	39.0
Lard	24.5	Lard	24.5	Lard	24.5
Corn starch	43.0	Corn starch	36.0	Corn starch	29.0
Salt mixture	4.5	Salt mixture	4.5	Salt mixture	4.5
Cod liver oil	3.0	Cod liver oil	3.0	Cod liver oil	3.0
	100.0		100.0		100.0
(7) About 61% Protein		Salt Mixture			
	Gm				
Casein	75.0	Calcium carbonate	134.8	Citric acid	111.1
Lard	17.5	Magnesium carbonate	24.2	Ferric citrate	6.34
Salt	4.5	Sodium carbonate	34.2	Potassium iodide	0.020
Cod liver oil	3.0	Potassium carbonate	141.3	Magnesium sulphate	0.079
		Orthophosphoric acid	103.2	Sodium fluoride	0.248
		Hydrochloric acid	53.4	Potassium aluminum sulphate	0.0245
		Sulphuric acid	9.2		

The beef muscle proteins used in the diets were obtained from a manufacturer who stated that the material was made from fresh lean beef, mechanically freed of fat, rapidly dried and ground to a powder. Our analyses of samples showed that it contained 12.5 per cent nitrogen and about 10 per cent of ether soluble substances. It was assumed that all of the nitrogen was in the form of protein ($N \times 6.25$) and that 100 Gm of the powder accordingly contains 78 Gm of protein.

Since the beef furnishes a physiologic mixture of inorganic salts, the amount of the artificial mixture used was decreased as the percentage of beef in the diet was increased.

The third group of diets, the composition of which is given, was employed to study the effect of vegetable proteins on the kidneys. Since the seeds used contain at most 25 per cent of protein, this method of feeding vegetable proteins does not permit the construction of a

diet containing enough of these proteins to test the question in hand unless they are incorporated in a diet which also contains some other protein in concentrated form. Diets of the type commonly used by McCollum⁴ were selected for this purpose, since his long experience has shown them to be adequate.

Diets Containing Beef Muscle Proteins

(8) About 12% Protein		(9) About 17% Protein		(10) About 24% Protein	
	Gm		Gm		Gm
Beef	14.8	Beef	22.3	Beef	31.0
Lard	24.5	Lard	24.5	Lard	24.5
Corn starch	53.7	Corn starch	46.7	Corn starch	38.5
Salt mixture	4.0	Salt mixture	3.5	Salt mixture	3.1
Cod liver oil	3.0	Cod liver oil	3.0	Cod liver oil	3.0
	100.0		100.0		100.0
(11) About 31% Protein		(12) About 38% Protein		(13) About 72% Protein	
	Gm		Gm		Gm
Beef	39.5	Beef	48.1	Beef	92.5
Lard	21.0	Lard	20.0	Lard	3.5
Corn starch	33.8	Corn starch	26.6	Salt mixture	1.0
Salt mixture	2.7	Salt mixture	2.3	Cod liver oil	3.0
Cod liver oil	3.0	Cod liver oil	3.0		
	100.0		100.0		100.0

Diets Containing Vegetable Proteins

(14) About 18% Protein		(15) About 25% Protein	
	Gm		Gm
Wheat	30.0	Wheat	30.0
Maize	22.0	Maize	20.0
Peas	20.0	Peas	18.0
Beans	20.0	Beans	15.0
Casein	3.5	Casein	12.5
Cod liver oil	2.0	Cod liver oil	2.0
Sodium chloride	1.0	Sodium chloride	1.0
Sodium carbonate	1.5	Sodium carbonate	1.5
	100.0		100.0
(16) About 32% Protein		(17) About 39% Protein	
	Gm		Gm
Wheat	20.0	Wheat	17.0
Maize	20.5	Maize	10.5
Peas	20.0	Peas	23.0
Beans	15.0	Beans	19.5
Casein	20.0	Casein	25.5
Cod liver oil	2.0	Cod liver oil	2.0
Sodium chloride	1.0	Sodium chloride	1.0
Sodium carbonate	1.5	Sodium carbonate	1.5
	100.0		100.0

In order to obtain information in regard to the effect of nucleoprotein on the kidneys, a group of diets containing beef liver is being fed. Results from the following diet are available for comparison with those obtained from the foregoing diets. Fresh beef liver is minced, spread in a thin layer in broad pans, dried at about 70 C and ground to a coarse powder.

⁴ McCollum and Simmons. *Newer Knowledge of Nutrition*, New York, The Macmillan Company, 1925.

The renal injury provoked by high protein diets might be caused by the extra work required of the kidneys in removing the unusually large amount of nitrogenous end-products. In order to increase the excretory work of the kidneys, urea in amounts sufficient to equal the nitrogen metabolism of a diet containing 40 per cent of protein was added to an otherwise normal diet. For this purpose, diet number 3 was used, and cornstarch was replaced by urea on the basis of the following calculations. A 40 per cent diet contains 64 per cent nitrogen and an 18 per cent casein diet, 2.88 per cent, therefore, 3.52 per cent nitrogen must be added. Urea contains 46.5 per cent nitrogen.

Accordingly, the inclusion of 7.57 Gm of urea in 100 Gm of a diet containing 18 per cent of casein will satisfy the requirements. The diet used is given as diet 19.

Diet Containing Beef Liver

(18) About 11% Total Nitrogen		
Liver		80.0 Gm
Lard		16.0 Gm
Salt mixture		1.0 Gm
Cod liver oil		3.0 Gm
		100.0 Gm

Diet with Urea Substituted for Cornstarch

(19)		
Urea		7.57 Gm
Casein		18.00 Gm
Lard		24.00 Gm
Corn starch		43.00 Gm
Salt mixture		4.50 Gm
Cod liver oil		3.00 Gm
		100.07 Gm

We have used two standard methods of obtaining evidence in regard to the state of the kidneys, namely, urinalysis and histologic examination. In an earlier paper, we described a simple apparatus⁵ for obtaining satisfactory samples of urine.

Both the experience in the clinic and that of laboratory workers, who have examined the urine of animals, has taught us that urine which contains neither albumin nor casts is coming from normal kidneys, and that the presence of much albumin and especially the occurrence of numerous casts is a reliable sign of disease of the kidneys. This latter statement, however, should be modified by noting several exceptions. Albuminuria without casts is found in human beings in the form of orthostatic albuminuria, and transient albuminuria may be

⁵ Curtis, A. C., and Newburgh, L. H. Toxic Action of Cystine on the Kidney, *Arch Int Med* 39:817 (June) 1927.

produced by violent exercise In experimental animals, the acidified urine often becomes opalescent or even cloudy on being boiled Those exceptional cases of albuminuria do not indicate disease of the kidneys, and accordingly makes the detection of albumin a less reliable sign of disease of the kidneys than the observation of casts The literature, however, does not contain any account of the occurrence of heavy albuminuria in the urine of laboratory animals the kidneys of which were free from disease After diligent search, a few investigators have noted one or two casts in the urinary sediment of laboratory animals the kidneys of which were assumed to be normal The easy detection of casts, however, is accepted as a reliable sign of renal abnormality

TABLE 1—*The Effect of Time and of the Amount of Protein on the Occurrence of Casts**

Per Cent of Protein	Days	60	120	180	300	360	420	480
8	V	V	V		IV			
	0	0	0		0			
12	X	V	V	IX	VIII	I	V	
	10	0	0	0	12†	0	20	
18	XVII	XIX	XV	XXI	XVIII	XI	VIII	
	0	5	7	9#	17‡	27	12	
25	XV	XXII	XXIII	XXII	XVII	X	VII	
	6	23	70	57	53	50	86	
32	XII	XVII	XXIV	XVIII	XXII	XII	X	
	0	41	79	66	91	100	100	
39	XII	XXVII	XXV	XX	XX	XIII	VII	
	17	55	92	100	100	100	100	
75	VIII	VIII	VIII	VIII		VI		
	100	100	100	100		100		

* The Roman numerals indicate the number of animals the urine of which was examined The Arabic numerals give the per cent of urines in which one or more casts were found

† The one animal of the group, the urine of which contained casts, also had hematuria At autopsy, infarction of the left kidney was found

One of the two animals of the group, the urines of which contained casts, was obviously ill It was found dead a few days later

‡ One of the three animals of the group, the urine of which contained casts, had an acute infection from which it died three hours after the urine was obtained

CORRELATION BETWEEN AMOUNT OF PROTEIN AND EXTENT OF RENAL INJURY

With this background in mind, we undertook routine examination of the urine of the animals for the presence of albumin and of casts We hoped thus to be able to answer in a broad way two questions 1 Is a high protein diet injurious to the kidneys of the rat? 2 If injurious, what is the largest amount of protein that may be habitually eaten without harming the rat's kidneys?

In table 1, we have brought together our observations in 565 twenty-four hour specimens The question of albuminuria is omitted for the sake of simplicity The animals are grouped according to the amount of protein contained in the diet, regardless of the kind The

table shows the number of animals from which specimens were obtained and how many of them contained casts. The urines were, as a rule, examined every second month. The animals used for this study were those that received diets numbers 1 to 17, inclusive. Thus, in the first table, protein is regarded as a single factor regardless of its type. The data contained in the table lead clearly to several conclusions. The percentage of animals, the urine of which contains casts, increases as the protein of the diet reaches the higher concentrations. Diets the protein content of which is 18 per cent or less exhibit only a minor and an irregular tendency to cause cylindruria. The factor of time is marked as an agency which increases the percentage of urines containing casts when the protein of the diet is 25 per cent or more, but appears to have only a trivial and irregular effect when the dietary protein is low.

The information contained in table 1 possesses an inherent weakness since it lacks the means of forming any opinion about the degree of

TABLE 2—*Relation between the Amount of Dietary Protein and the Number of Casts and Per Cent of Albumin in the Urine*

Per Cent of Dietary Protein	240 Days			480 Days		
	Animals, Number	Albumin, per Cent	Casts, Number	Animals, Number	Albumin, per Cent	Casts, Number
12	3	0	0	5	0.2	4
18	11	0	3	10	0	4
25	8	0	0	6	0.6	83
32	7	0	44	12	0.8	351
39	9	0.2	52	10	0.4	652
75	15	0.3	1,412	4*	1.4	4,705

* Only two animals in this group were alive at 480 days. The averages recorded in the table were obtained from counts made on the 410th day.

injury caused by the protein. The difference between urines recorded as normal and abnormal might be only one cast, in which case the injury would be negligible, or, 1,000 casts would be indicative of a significant amount of injury. In order to overcome this difficulty, the casts have been counted in a considerable number of urines by the method described by Addis.⁶ The percentage of protein in the same specimens has been determined by the method of Folin.⁷

Table 2 shows the average number of casts and the average amount of albumin in the twenty-four hour samples of urine in relation to the concentration of protein in the diet and the duration of the feeding. When the number of casts is used as a measure of renal injury, it becomes evident that diets containing 12 and 18 per cent of protein are harmless. Twenty-five per cent of protein causes a small injury if the diet is continued more than a year. Thirty-two and thirty-nine per

6 Addis T. Clinical Classification of Bright's Diseases, J. A. M. A. **85** 163 (July 18) 1925.

7 Folin J. Biol. Chem. **18** 283, 1914.

cent of protein cause the appearance of an abnormally large number of casts in eight months, and the injury becomes slowly more marked during the second eight months. When the diet contains 75 per cent of protein, the injury is well established in eight months and increases greatly during the subsequent months.

CORRELATION BETWEEN KIND OF PROTEIN AND EXTENT OF RENAL INJURY

The data dealt with thus far show clearly that the degree of damage to the kidney (measured by the urinary observations) is determined by the amount of protein in the diet for similar intervals of time. We wish now to bring forth evidence intended to show how greatly the degree of nephropathy depends on the kind of protein ingested.

TABLE 3—*Relation between the Type of Protein and the Degree of Renal Injury when the Protein is One Third of the Diet*

	240 Days		450 Days	
	Albumin, per Cent	Casts, Number	Albumin, per Cent	Casts, Number
Casein	0.1	37	0.1	312
Beef muscle	0.3	60	1.1	1,444

TABLE 4—*Relation between the Type of Protein and the Degree of Renal Injury when the Protein is Three Fourths of the Diet*

	240 Days		450 Days	
	Albumin, per Cent	Casts, Number	Albumin, per Cent	Casts, Number
Casein	0.2	783	0.5	992
Beef muscle	0.5	2,130	1.5	5,900
Liver	3.0	8,900		

Table 3 gives the average per cent of albumin and the number of casts in twenty-four hour specimens of urine for groups of rats, one third of whose diet consisted either of casein or of lean beef muscle.

Table 4 is constructed in the same way to compare casein, beef muscle and liver when approximately three fourths of the diet is protein.

These two tables bring out the fact that the nature of the protein fed is at least as important a factor as the amount of protein in both the production of injury and in the degree of injury. This statement derives further support from the course of events in the case of the rats that received the liver diet. These five animals, all of which showed the heavy albuminuria and the great numbers of casts, were unable to survive the diet a year. Four of them lived eight months and the fifth one, eleven and one-half months. Their early failure seemed the more significant, since they grew more rapidly and reached a greater weight than any other group studied.

The importance of taking the nature of the protein into account is likewise strongly emphasized by a comparison of the histologic changes caused by the different proteins⁸

Thus, the only injury obtained by us with casein was restricted to the tubules. In animals that received diets containing 75 per cent of casein for more than a year, the tubules contained numerous casts and there was moderate degeneration of the epithelium of the convoluted tubules and some tubular dilatation.

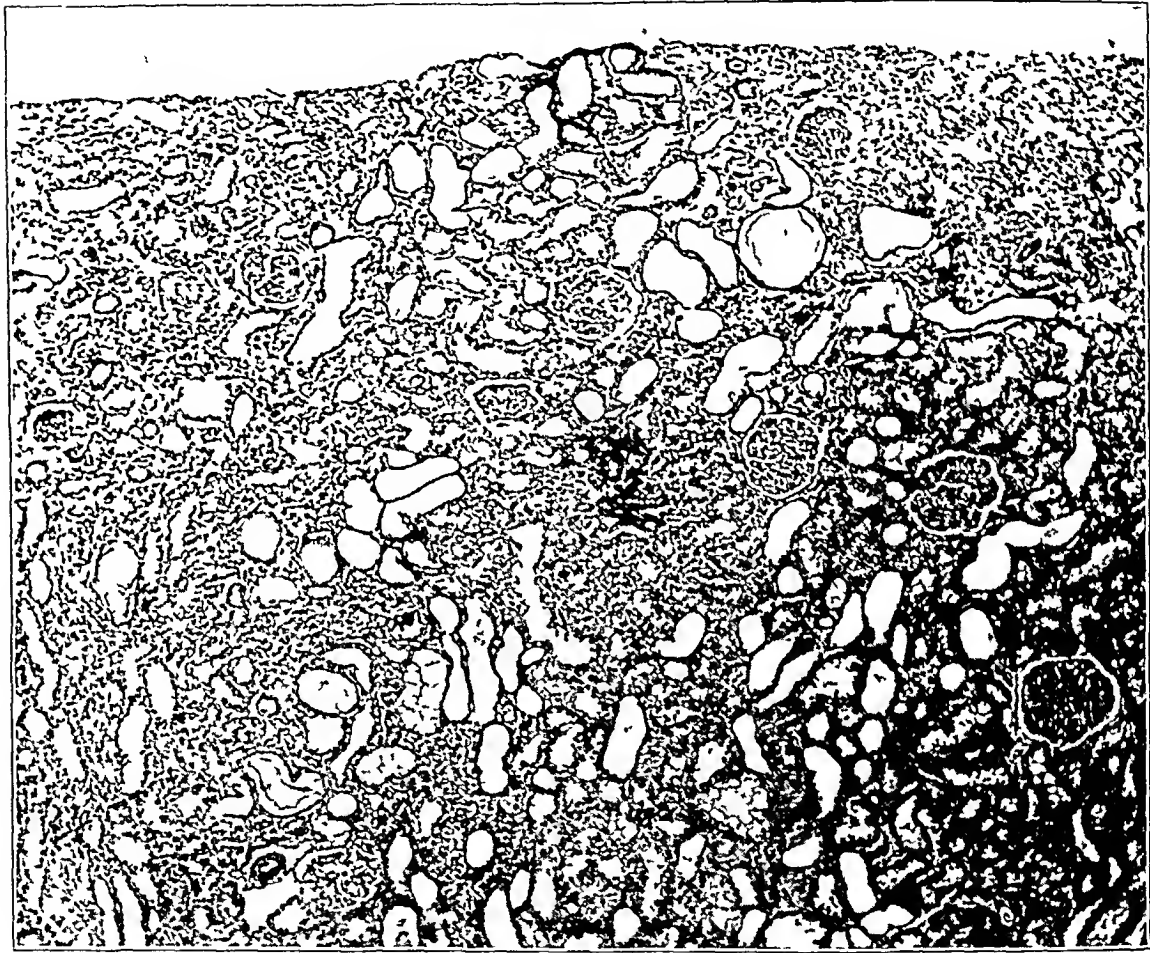


Fig 1—Diffuse tubular dilatation and atrophy, and many casts. This rat ate a diet containing 31 per cent of beef muscle proteins for fifteen months.

Beef muscle proteins, in addition to causing a more severe tubular injury, are capable of injuring the glomeruli and of causing a patchy fibrosis. Figure 1, which is a photomicrograph from a rat that had

⁸ For microscopic study, we used only kidneys from animals that were killed by a blow on the head. Immediate autopsy was performed, and the tissues were hurried into formaldehyde solution, thus, any possible confusion due to postmortem change was avoided. The standard technic for paraffin sections was followed. The sections were stained with hematoxylin and eosin.

eaten a diet containing 31 per cent of beef proteins for fifteen months, showed more tubular injury than was found in animals that had taken the diet containing 75 per cent of casein for the same length of time. Figure 2 shows glomerular damage from 31 per cent of beef muscle proteins in eighteen months. Definite glomerular lesions were not seen in any of the rats the diet of which contained less than 31 per cent of protein nor in any of the casein series, including even the rats that took diets containing 75 per cent of casein. When the rats live on diets containing 38 per cent of beef muscle proteins for more than one year, a

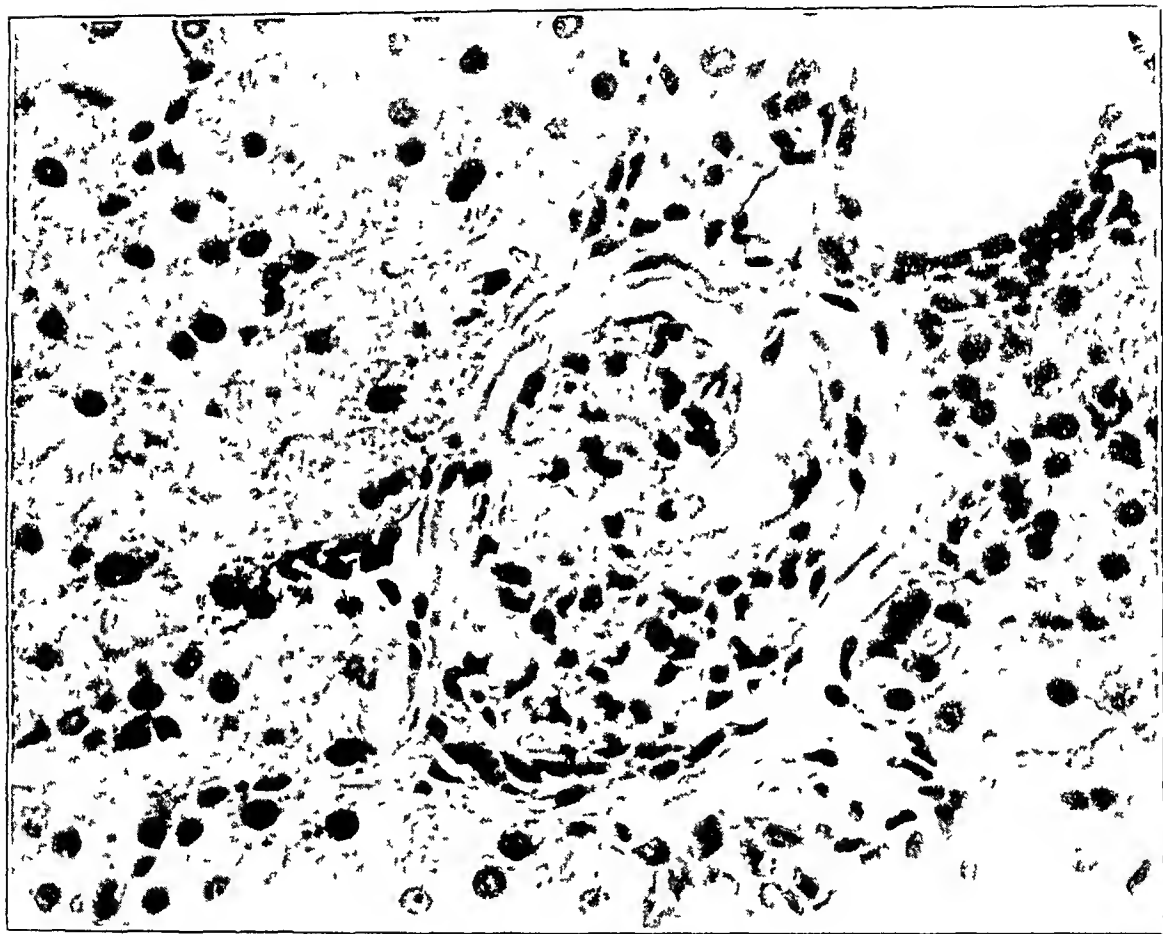


Fig 2—Marked thickening of Bowman's capsule, from a rat that took the diet containing 31 per cent beef muscle proteins for eighteen months

third sign of renal injury appears. Figure 3 is from an animal that was killed after thirteen months of such a diet. The photomicrograph shows one of a number of small patches of fibrosis in addition to glomerular and tubular abnormality. The kidneys of old rats frequently show scattered minute areas of fibrosis. Osborne, Mendel, Park and Winternitz called attention to this increase in connective tissue in rats more than 500 days old, but that were otherwise presumably normal. Figure 3 is from an animal 420 days old. The fibrotic areas seen in sections of kidneys from rats that had received the diet containing 38 per

cent of beef muscle protein for from 420 to 450 days, were much larger and more numerous than those found by us in some of the rats of equal age, the diets of which contained 18 per cent of casein or beef muscle protein. Diets containing 72 per cent of beef protein are capable of causing a considerable degree of fibrosis. Figure 4 shows one of a number of such patches. This rat had been on the high beef diet 470 days when he was killed. The kidneys of the large number of rats that had received diets containing 18 per cent of protein or less were, in general, free of fibrotic areas. In a few instances, occasional minute patches

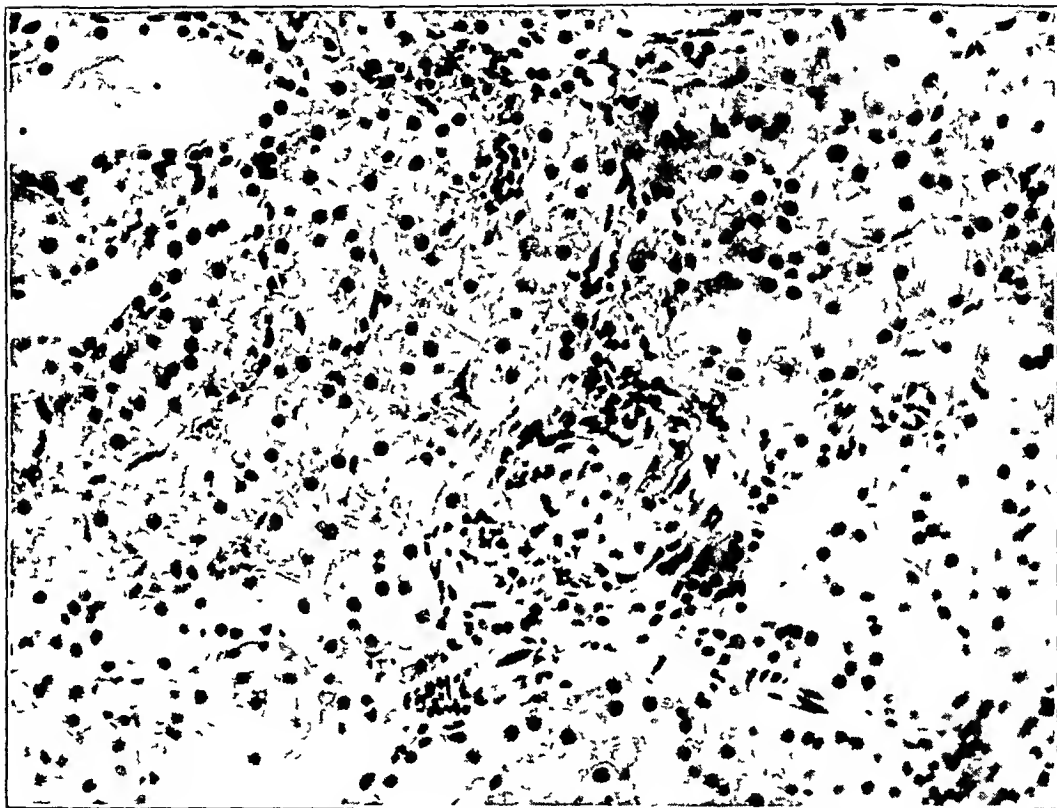


Fig 3—A small patch of fibrous tissue partially obliterating the glomerulus. This rat received a diet containing 38 per cent of beef muscle proteins for fourteen months (420 days)

of cellular increase were noted, they were never large enough to occupy more than a portion of a high power field, and never caused thickening of Bowman's capsule or injury of the tubules separated by the new cells. The area reproduced in figure 4 is one of many found in the rats that had taken the 72 per cent beef protein diet for more than one year. The large size of this area contrasts sharply with the smallness of the foci seen in the low protein animals, there is at least a ten-fold difference. Figure 5 shows in more detail, the partial fibrosis of the glomerulus and the destruction of the tubules in one part of a fibrotic patch.

None of the casein or beef diets caused changes sufficiently great to definitely alter the gross appearance⁹ of the kidneys. However, when the diet contains 75 per cent of beef liver, the appearance of the kidneys is strikingly altered. In so short a time as 300 days, the outer surface of the kidneys had everywhere become markedly granular and the color had changed from the normal red-brown to gray-yellow, mottled with spots of purple. Figure 6 is a photograph of a normal kidney and figure 7, the kidney of a rat that was killed after it had eaten the liver diet for ten months. The granular character of the latter is evident. Figures 8, 9, 10 and 11 are microscopic views of the

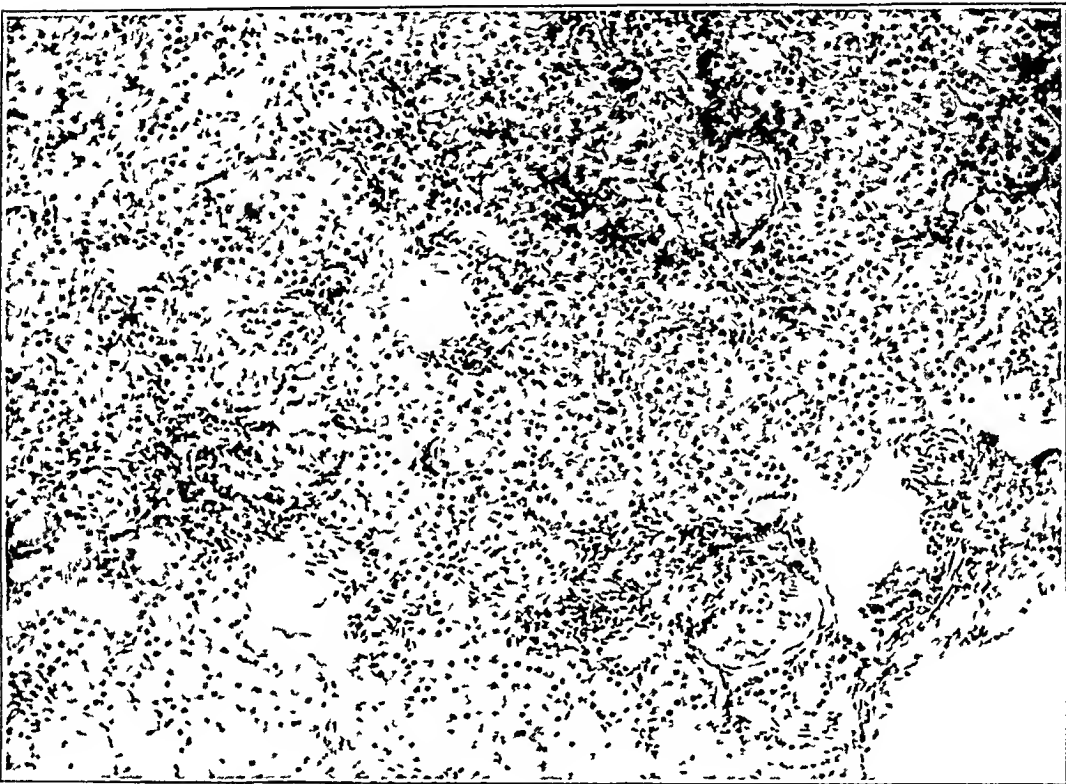


Fig 4—Area of patchy fibrosis concentrated about the glomeruli. From a rat that ate a diet containing 72 per cent of beef muscle proteins for sixteen months.

⁹ The kidneys of rats on the higher levels of protein were larger than those of animals the protein intake of which was less. Averages from four diets are contained in the accompanying table.

Our observations agree with those of earlier observers who pointed out that the weight of the kidney is related to the amount of protein in the diet. Moise and Smith (*Arch Path* 4:530 [Oct] 1927) published the most recent work dealing with the character of this increase in weight.

Per Cent of Protein	Kidney Weight, Gm	Kidney Weight Body Weight
18	1.7	0.82
25	1.7	0.80
32	2.4	0.89
39	2.5	0.99

kidney of a rat that was killed when he had taken the liver diet for 350 days. The great increase in connective tissue, especially in the labyrinths, which causes contraction of the kidney in these areas, is well seen in figures 8 and 9. The marked cystic dilatation of some of the tubules, a well-known feature in chronic nephritis of man, is likewise clear. Various forms of glomerular injury may also be seen, namely, great thickening of Bowman's capsule by layers of connective tissue, adhesions between the capillary tufts and the capsule, lobulation of the glomeruli and fibrosis of some tufts.

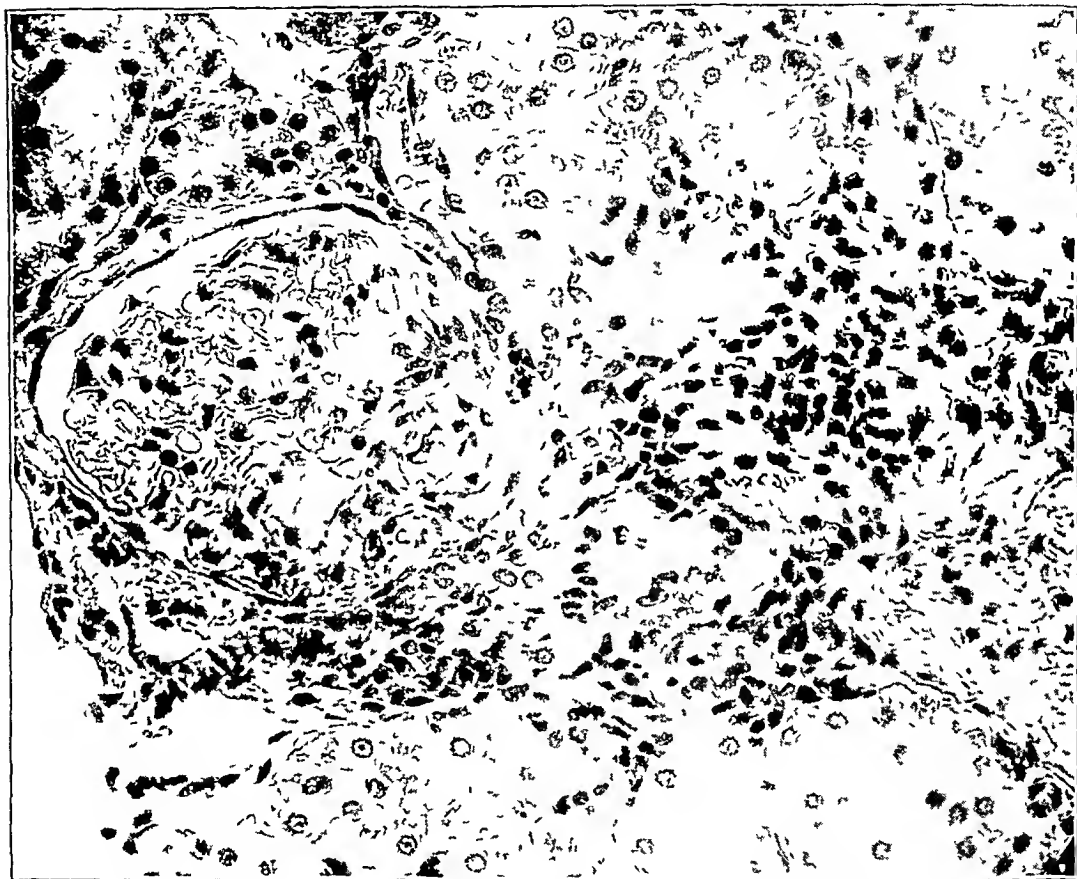


Fig 5—Partial fibrosis of a portion of the glomerulus and the destruction of the tubules in one part of a fibrotic patch. Occasional red blood cells are seen in the area. This is part of the field shown in figure 4.

The renal lesions that have been described are not due to a dietary deficiency, for the diets that caused the most injury also permitted the best growth. Inspection of figure 12 will show that the groups of rats that ate the high beef diets and the liver diet, grew more rapidly than did the animals on which Donaldson's standard growth curve is based. On the other hand, the animals the diets of which were too low in protein to permit growth at the normal rate had normal kidneys.

REVIEW OF LITERATURE

The foregoing experiments have convinced us that the injuries to the kidney described were caused by the protein of the diet and that the degree of injury depends on the concentration of the protein, its type and the duration of the feeding. While we were carrying on our experiments, a number of papers dealing with this subject appeared



Fig 6—Normal kidney showing the smooth surface and the mottling due to the stellate veins

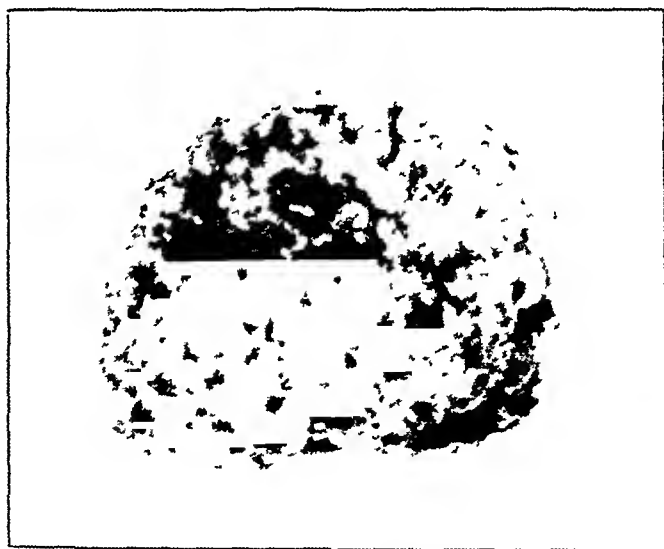


Fig 7—Kidney from a rat that ate a diet containing 75 per cent of dried beef liver for ten months, the same enlargement as figure 6. The surface is everywhere coarsely and finely granular, and the normal venous markings have disappeared

Some observers reported results similar to ours, while others did not see any evidence of the deleterious effect of protein on the kidneys. The three papers of Drummond, Crowden and Hill,¹⁰ Reader and

¹⁰ Drummond, J. C., Crowden, G. P., and Hill, E. L. G. *J. Physiol.* 56: 413, 1922

Drummond,¹¹ and of Kennedy¹² may be dealt with together. The primary interest in each is the effect of a high protein diet on reproduction and growth. A diet containing about 75 per cent of casein was used to test the influence of an excess of protein. The rats were killed after they had been on the diet four months. The urine was not examined. The kidneys did not show any microscopic abnormalities. This outcome convinced these authors that high protein diets do not injure the kidneys of rats. This generalization is not warranted by the data in their

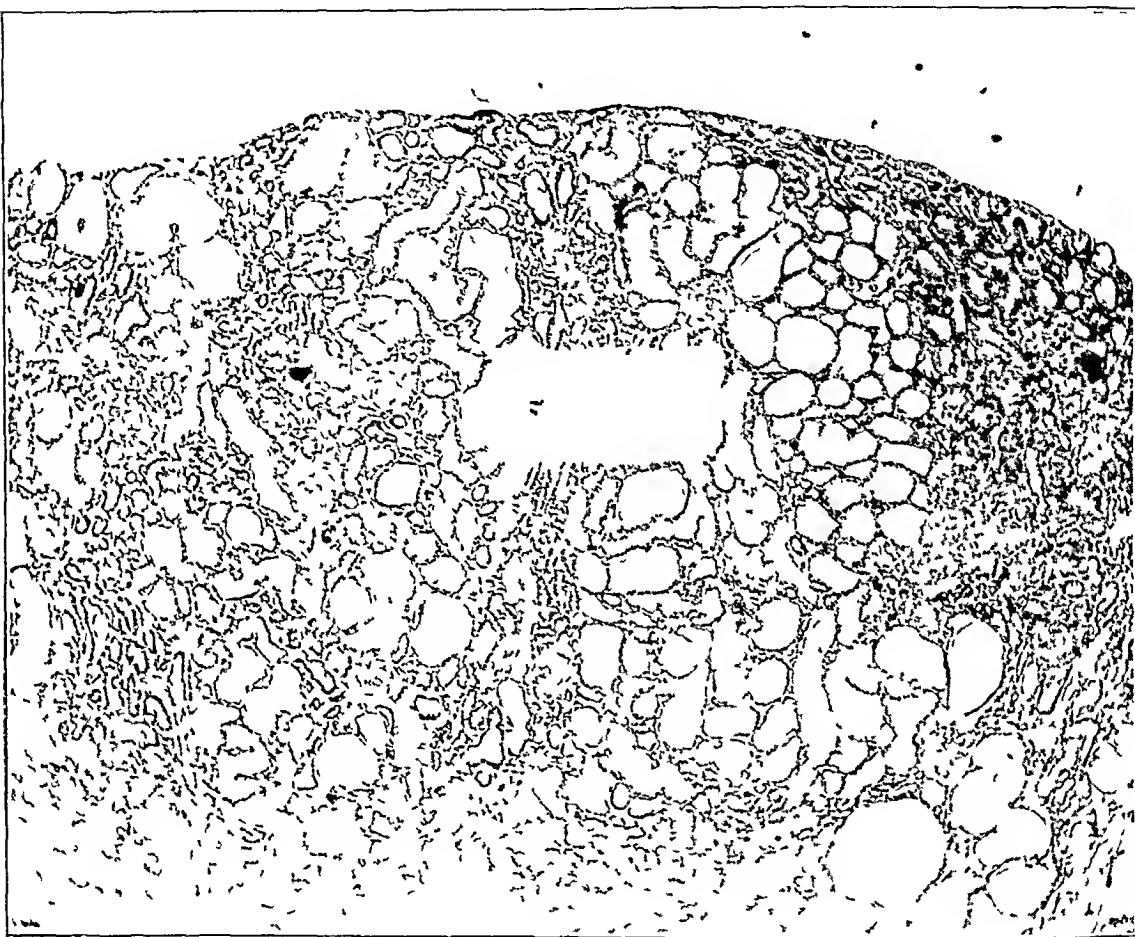


Fig 8—A low power view of a section of kidney from a rat that took a diet containing 75 per cent of dried beef liver for twelve months. Showing the bands of contraction most marked in the labyrinths, and the general dilatation of tubules in the intermediate areas.

possession. They were justified merely in stating that a high casein diet did not produce histologic changes in the kidneys when the animals were fed for the brief period of four months. Had they published such a statement, they would have found themselves in entire agreement

11 Reader, V. B., and Drummond, J. C. *J. Physiol.* **59**: 472, 1925.

12 Kennedy, W. P. *Quart. J. Exper. Physiol.* **16**: 281, 1926.

with us Casein, as we have already pointed out, produces only a small amount of injury and must be fed in large amounts for a least one year in order to obtain microscopic evidence of damage

Addis, MacKay and MacKay¹³ fed a group of rats a diet containing 74 per cent of casein for 330 days They considered the kidneys histologically normal and found no more casts in the urine of the animals on the high diet than in that of the controls A careful comparison of their method of examining the urine with ours suggests why they did not find an abnormally large number of casts in the case of the rats fed

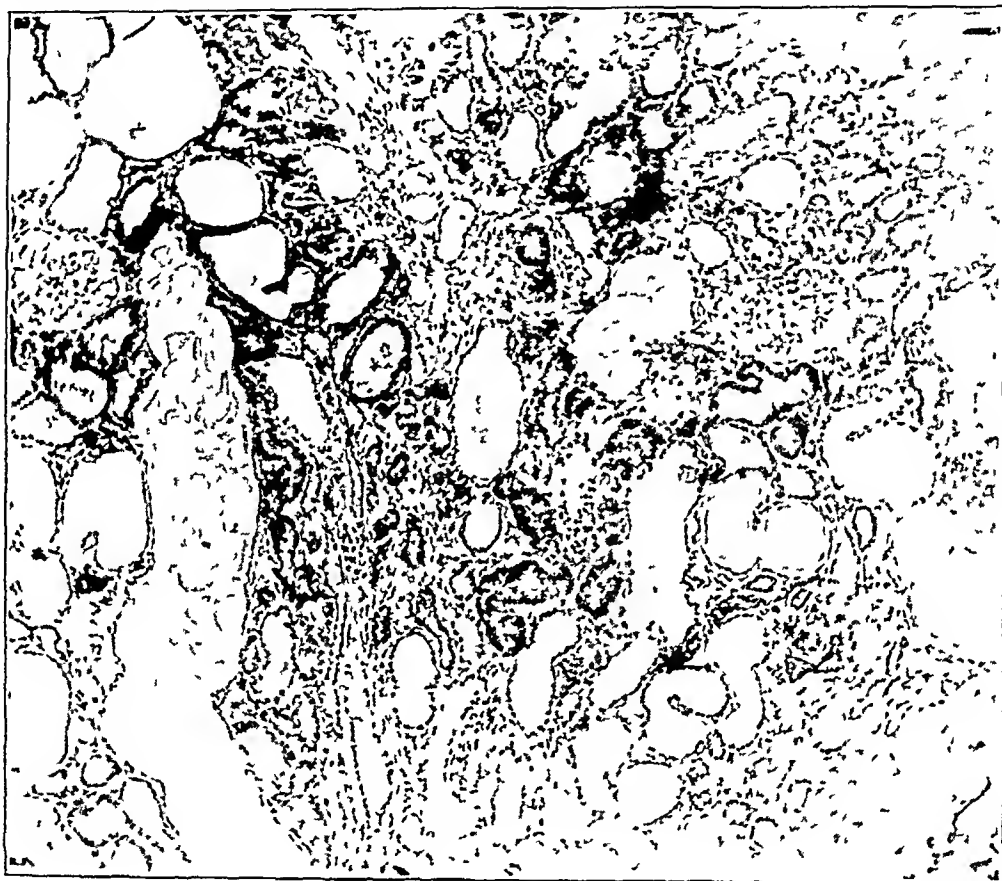


Fig 9—A higher power view from the same kidney as figure 8, to show a band of contraction in which glomeruli are not visible The dilated and atrophied tubules are widely separated by the connective tissue

on a diet high in casein We collected urine for twenty-four hours, centrifugalized the whole specimen and pipetted off the supernatant fluid down to 0.1 cc All the casts voided in twenty-four hours were thus collected in 0.1 cc A drop of this mixed urine was placed on a counting chamber and 1 c mm counted We found, on the average, eight casts in 1 c mm in the urine thus prepared from rats that had received 75

¹³ Addis, T MacKay, E M, and MacKay, L L J Biol Chem **71** 139, 1926

per cent of casein for ten months. Addis and his co-workers, on the other hand, obtained fresh urine by causing the rat to inhale a whiff of ether. They stated that a specimen so obtained has one-tenth the volume of the twenty-four hour amount. If their rats voided casts at the same rate as ours, their fresh specimen would contain eighty casts. Since their method of counting is the one used by us, they should have found less than one cast in the 1 c mm counted. We believe that this difference in procedure is the basis for their statement that "An occasional cast

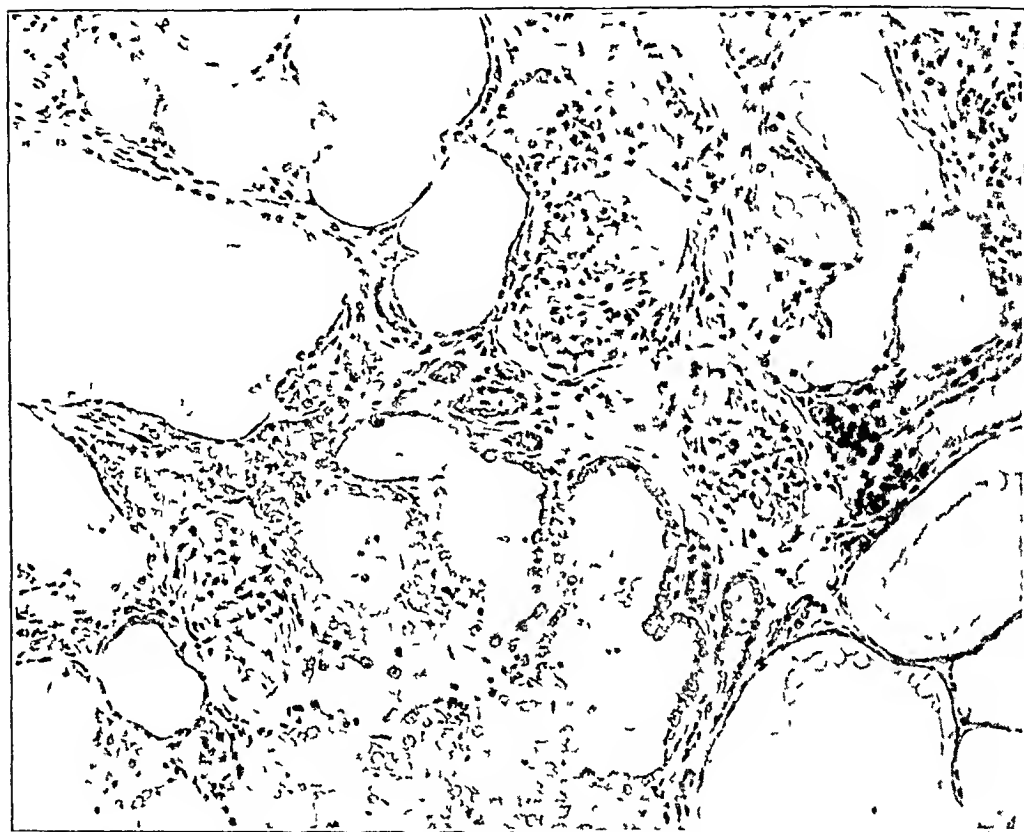


Fig 10—A still higher magnification of the section presented in figure 9, to show the thickening of Bowman's capsules with extension of the connective tissue into the capillary tufts, and the cystic dilatation of tubules the lining of which resembles pavement epithelium

was found at one time or another in the urine collected from nearly all of the experiments. They were no more frequent in the high protein than in the control groups."

Jackson and Riggs¹⁴ likewise studied the effect of a diet containing 76 per cent of casein on the kidneys of rats. In regard to urinalysis they state

14 Jackson, H, Jr, and Riggs, M D. *J Biol Chem* 67 101, 1926

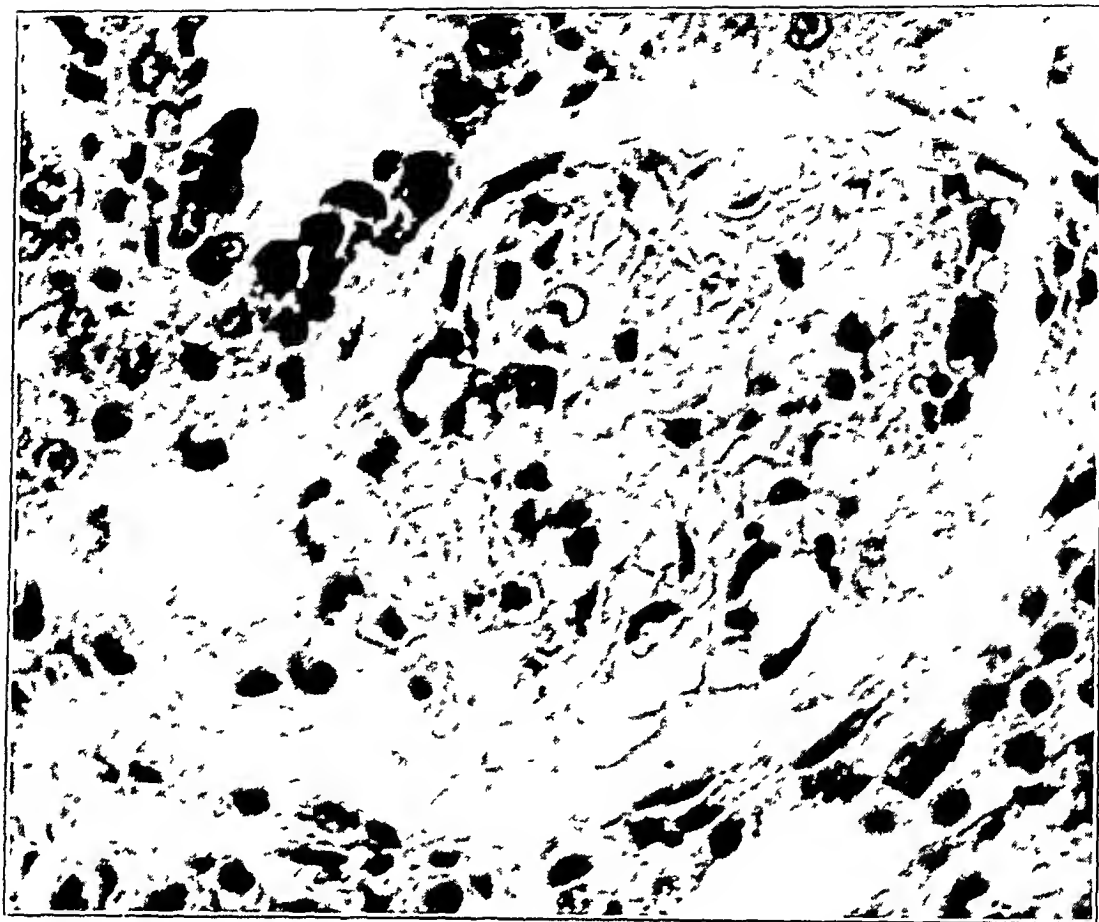


Fig 11—High power magnification of a glomerulus from the same kidney to show hyaline thickening of the capsule, adhesions of the tuft to the capsule and the partial obliteration of the capillary tuft

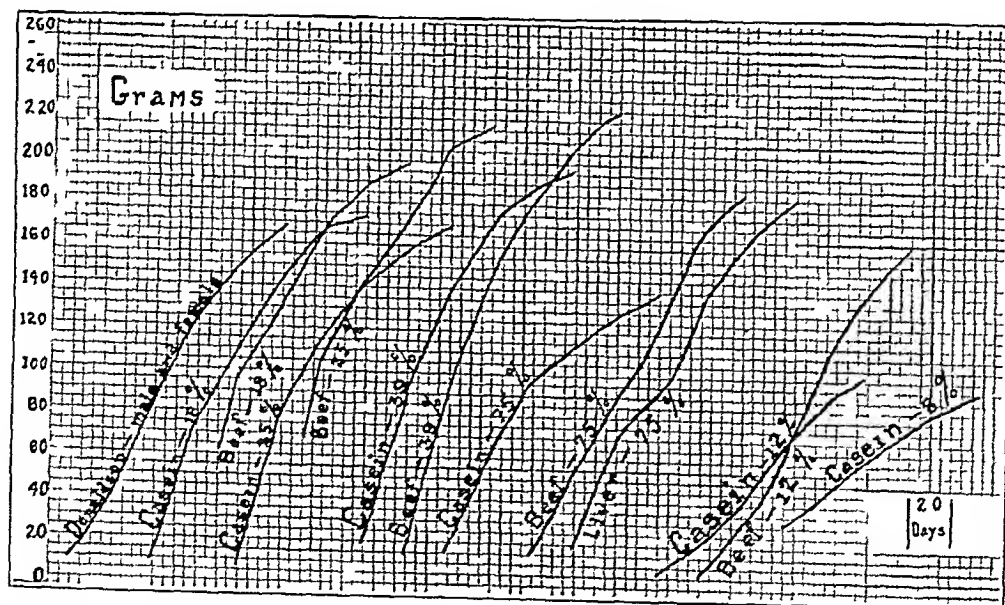


Fig 12—Growth curves The diets which caused the greatest renal damage were adequate for normal growth

During the progress of the experiment, each rat was periodically placed in a metabolism cage and urine collected. Normal rats do not show casts or red cells. Casts were not found in any of the specimens except rarely in one of the rats on high protein plus alkali.

In the absence of any detailed description of the method for obtaining specimens, we are left with the question whether casts would not have been found in the urines of the rats on the high casein diets, if more care had been taken in the collection and preservation of the specimens. These investigators were also unable to detect any histologic abnormalities in the kidneys from rats that had eaten the excessive amounts of protein for more than one year.

Jackson and Riggs also fed two rats a diet containing 20 per cent of casein and 56 per cent of egg albumin, with negative results. This diet failed to cause hypertrophy of the kidneys—a change which was caused by their high casein diet and the response, to a variety of high protein diets, obtained by all observers who have weighed the kidneys. Furthermore, the daily urinary nitrogen from the two rats receiving egg albumin was 0.95 Gm, whereas the average from the high casein group was 1.21 Gm. This difference corresponds with the differences in ingested nitrogen. The casein group took 0.631 Gm per hundred grams of body weight, but the rats that received egg albumin took only 0.525 Gm nitrogen per hundred grams. The less intense nitrogen metabolism in these latter rats may, in part, account for the absence of signs of injury.

Osborne, Mendel, Park and Winternitz¹⁵ likewise stated, in several preliminary reports, that high casein diets did not injure the kidneys of rats. Only five of the large number of rats fed the casein diets by them were kept on the diet more than 300 days, and in no case did the experiment last 350 days. When the positive results, reported by Polvogt, McCollum and Simmonds,¹⁶ became known to them, they noted that these workers had used a different type of diet and had fed their animals much longer. They accordingly fed a similar diet, the composition of which is as follows, to six rats, for 400 days or longer: Wheat, 30 Gm, corn, 20 Gm, casein, 20 Gm, liver, 20 Gm, navy beans, 7.5 Gm, calcium carbonate, 1.5 Gm, and sodium chloride, 1 Gm.

Furthermore, to control the old age factor, they secured a group of rats, 500 days, or more, of age. These animals had been fed a stock diet containing the usual moderate concentration of protein.

From the detailed account of the histologic study of the kidneys of 200 rats, ninety-two of which had been on diets rich in protein from

¹⁵ Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C. *Am J Physiol* **72**: 222, 1925.

¹⁶ Polvogt, L. M., McCollum, E. V., and Simmonds, N. *Bull Johns Hopkins Hosp* **34**: 168, 1923.

seven to 400 days and 108 of which were controls, we consider the following sentences significant ¹⁷

In many rats on the very rich protein diets, the dilatation of the tubules was marked enough to enable us to guess correctly at a glance the high protein nature of the feeding. Dilatation of the tubules was not present or, at least not clearly recognizable, in the sections of other rats which were either on the high protein diets for short periods or else on diets in which the proportion of protein was not particularly large.

Some rats on the high protein diets showed actual lesions. In certain of the control animals, lesions of an exactly similar nature were found.

Eighteen rats on the high protein diets showed these lesions, the remaining eighteen, on very high protein diets, did not. The lesions were severe in five of the six rats that had been on the Polvogt, McCollum and Simmonds diet 400 days. Among the control rats, the kidneys of only five were affected. All were 515 days old, or older. The lesions were of the same type as those seen in the Polvogt, McCollum and Simmonds diet.

It is conceded by Osborne, Mendel, Park and Winternitz that the dilatation is caused by the diets rich in protein, and that animals on such diets develop focal lesions much more frequently and earlier than the controls. But these authors appear to be in doubt in regard to the significance of these histologic departures from the normal. We interpret them as evidence of the harmful effect of high protein diets, and especially so, since the severe focal lesions were found in the group of rats that received a diet containing 20 per cent of liver.

If this latter group is left out of consideration it will be realized that the views expressed by the writers of the papers discussed thus far were derived from their experience with casein. From what has already been said about casein, it is not difficult to understand how they reached the conclusion that high protein diets are not harmful to the kidneys. But our own experiments show clearly that it is not permissible to generalize about protein as if it were an entity. The most that can be learned from the experiments of these writers, if their work is accepted without any deduction, is that diets rich in casein do not injure the kidney. But the information obtained about casein must not be transferred to protein in general. A sharp distinction must be made between the phrases "high casein diets" and "high protein diets," for we have shown that certain other proteins produce an unmistakable nephropathy.

It is for that reason, we believe, that both Evans and Risley ¹⁸ and Polvogt, McCollum and Simmonds obtained injury to the kidney from the diets used by them. The composition of the diet used by the latter workers has already been given. Their rats were killed when they had eaten the food 400 days. In summarizing their experiments, they state

¹⁷ Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C. *J. Biol. Chem.* **71** 317, 1927.

¹⁸ Evans, N., and Risley, E. H. *California & West Med.* **23** 437, 1925.

"All the rats fed the diets high in protein had lesions of the kidneys of considerable severity. On the other hand, animals of middle age from the breeding stock all had essentially normal kidneys." Evans and Risley used proteins from several sources including meat, peanuts, soy beans and wheat gluten. These investigators took the precaution to send the animals to the pathologic laboratory, identified by number alone, so that the one who made the histologic examination of the kidneys did not have any knowledge of the diet the animal had received. They found that animals fed on high protein rations for prolonged periods showed nephritic changes without exception.

Finally, Moise and Smith¹⁹ accentuated any effect of diet by unilateral nephrectomy. Such animals were fed either an 18 per cent or an 85 per cent casein diet. They did not observe any significant anatomic evidence of renal injury in the animals on the "standard" diet. In animals that had been on high casein ration for 90, 120 and 150 days after nephrectomy, however, "significant" glomerular and tubular changes were found without exception. The lesions were not merely isolated focal changes but were conspicuous and relatively widespread. They included proliferation of the epithelium of Bowman's capsule, adhesions between the tuft and capsule, fibrous thickening of the capsule, partial fibrosis of the tuft, degenerative changes in the tubular epithelium and areas showing an increase in the interstitial tissue. They also found casts and a markedly increased amount of albumin in the urines of rats on the high casein diet, after eighty-eight days. These experiments show that severe kidney disease may be caused in a relatively short period of time by a protein even as mildly irritating as casein, when its effect is borne by only one kidney.

The renal injury that is caused by diets containing an excess of protein might be brought into existence in many ways. Addis¹³ has shown that it is not due to a change in the hydrogen ion concentration of the urine. One of us (L. H. N.)¹ was unable to find any of the dietary protein in the blood or urine. No one has demonstrated the presence of toxins in the systemic circulation, resulting from bacterial decomposition of the protein in the intestines. The addition of large amounts of urea to an otherwise normal diet to increase the excretory work of the kidneys failed to cause hypertrophy in the hands of Osborne, Mendel, Park and Winternitz, Hinman,²⁰ or Addis, MacKay and MacKay.

COMMENT

Our own urea diet number 19, which caused the rat to excrete an amount of urinary nitrogen equivalent to that yielded by a diet containing 40 per cent of protein, was fed to a group of rats for one year. In

19 Moise, T. S., and Smith, A. H. Effect of High Protein Diet on Kidneys, *Arch. Path.* 4: 530 (Oct.) 1927.

20 Hinman, F. *J. Urol.* 9: 289, 1923.

no case did we obtain evidence from the urine, or by microscopic examination of the kidneys, that the prolonged excretion of this large amount of nitrogen was harmful to the kidneys, nor did this diet in which the urea content was high cause any enlargement of the kidneys. The increase in size caused by high protein diets is apparently something more than a response to increased activity. It appears to have a more specific cause.

Positive evidence dealing with the mechanism of the protein injury has been obtained by studying the effect of the amino-acids. Our injection²¹ and feeding experiments⁵ have shown that some of the amino-acids resulting from the digestion of protein are nephrotoxic. We obtained the most striking evidence of injury from the injection of cystine and of tryptophan. Casein is low in these amino-acids, whereas muscle protein is relatively rich in both of them. We believe that these differences in the amino-acid make-up of these two proteins is, at present, the best explanation for the difference in the degree of nephrotoxicity shown by them.

SUMMARY

The effect of diets containing several different proteins in varying concentrations on the kidneys of the white rat has been studied. Casein, beef muscle, beef liver and the seeds of cereals and legumes were used as the sources of the proteins.

It was found that the degree of injury was determined by the type of protein, its concentration and the length of the feeding.

The character of the protein is more important than either of the two other factors.

Diets containing 75 per cent of dried liver produce a granular kidney in less than one year, but the same amount of casein, fed sixteen months, causes only a moderate tubular injury. The effect of a similar amount of beef muscle is intermediate between these two. The surface of the kidney remains smooth, but microscopic sections show numerous areas in which seriously injured glomeruli and necrotic tubules are embedded in fibrotic tissue.

²¹ Newburgh, L. H., and Marsh, P. L. Renal Injuries by Amino-acids, *Arch Int Med* **36** 682 (Nov) 1925.

GENERALIZED GRANULOMATOUS LYMPHADENITIS ASSOCIATED WITH DIFFUSE PROGRESSIVE FIBROSIS OF THE LUNGS*

CHARLES L CONNOR, M D

BOSTON

It is thought that the following case should be recorded because of the apparently unique combination of lesions which were severe enough to cause death. It needs little comment. It does not resemble any other disease entity which I have been able to find, but, on the contrary, the clinical signs and symptoms are so clearcut that it seems to present an entity in itself. The clinical course and pathologic observations do not correspond with any clinical or pathologic condition within the knowledge of a considerable number of clinicians and pathologists who have seen the case. But because of these clearcut features, a similar case in the future might be recognized in time to permit a more complex study of the condition. I have been unable to find anything remotely resembling it in the literature. As complete a description as possible is therefore given, only impertinent details being omitted.

REPORT OF CASE

Clinical History—A boy, aged 16, entered the Montreal General Hospital, March 2, 1927, in the service of Dr C P Howard, complaining of a lump in the left groin, slight cough and vague pain over the pit of the stomach. He had one brother and five sisters, who were alive and well, his parents were also well. With the exception of the common childhood infections, he had not had any serious illness. Three weeks before admission, while playing, he had struck his left groin with the edge of a chair. The immediate pain was slight and transient, and he continued work as a check-room boy. Two days after the injury, he began to have frequency and urgency of urination, and a lump was discovered in the left groin on the following day. He continued work, but five days after the injury, the lump became painful, and it was found that the temperature was elevated. Little could be found out about the patient's condition during the eleven days previous to admission to the hospital, except that deep respirations had caused pain in the region of the umbilicus, that he had contracted a slight cough and that he had had fever and, for the last four or five nights, night sweats. The pain in the groin had disappeared.

Physical Examination—On admission, the patient had a hacking cough with little sputum, vague pain in the epigastrium, and generalized glandular enlargement, including the cervical, axillary, epitrochlear and inguinal glands. No single gland felt larger than 2 cm in diameter. The largest mass in the left groin formed a nodular group from 3 to 4 cm in diameter.

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The tonsils were not visibly enlarged, the throat was normal. There was dulness to percussion on the right side in the axilla, and from the scapula to the base, impaired resonance was also noted at the base of the left lung. A friction sound was heard at the bases of both lungs, and many crepitant râles on both sides, low, and in the axilla on the right. There was some retrosternal dulness. The heart was not enlarged, and murmurs were not heard. The spleen was readily felt, it had a thin, sharp edge. A few red spots were present on the thorax, which were palpable, these did not resemble rose spots. The pulse rate was 100 and was dicrotic and regular. The temperature was 102 F. The blood count revealed red cells, a normal number, white cells, 17,400 with 80 per cent polymorphonuclears. The urine was normal for albumin, sugar and casts, the specific gravity was 1.012. The Wassermann reaction was ++++. Examination of the sputum, which was small in amount, showed it to be blood tinged, tubercle bacilli were not present, a few diplococci were found. A mouse that was given intraperitoneal injections remained well, it was killed and no exudate was found. Culture of the blood did not show growth in four days. The x-ray diagnosis (Dr W. L. Ritchie) was as follows: "There are shadows throughout the lungs, particularly the bases, suggestive of infiltration due to tuberculosis. No evidence of any fluid. No mediastinal thickening. Heart normal in size, shape and position." The clinical impressions were acute pneumonic phthisis with tuberculous adenitis, infectious mononucleosis or a lymphatic tumor. The Pirquet reaction was negative. A second blood count showed red blood cells, 5,150,000, white blood cells, 19,800, polymorphonuclears, 88 per cent, lymphocytes, 11 per cent, large mononuclears, 1 per cent, platelets, 240,000, and reticulated red cells, 0.5 per cent. Two other counts gave similar results.

There were few other symptoms. The temperature ranged from 99.6 to 104 F, the pulse rate from 100 to 140, and the respiratory rate from 20 to 40, most of the time it was about 28. A second Pirquet reaction was negative. The dulness in the lung spread so that latterly the signs were those of a bilateral lobar pneumonia. The temperature dropped, the pulse rate mounted, and the patient died eleven days after admission, after an illness lasting thirty days.

Autopsy—Autopsy was performed six hours after death. The body was that of a slender boy, whose stated age was 16, but who looked two years younger. It was well developed and well nourished, but there was no pubic hair, and little hair over the chest and axillae. The body measured 153 cm in length. There was no rigor mortis or edema, and only slight lividity of the dependent parts. There was an abraded, reddened area about 4 cm in diameter over the point of the right elbow. The scalp, eyes, ears, nose and mouth were normal. The pupils were equal and measured 7 mm. A comparatively large lobulated mass of nodes could be palpated in the inguinal regions of both sides. Smaller palpable nodes were present in each axilla and in the neck. The thyroid was not enlarged. The genital organs were small. The skin was smooth, pale and elastic. The subcutaneous fat measured about 1 cm and was of normal color.

The peritoneum was moist throughout, and about 300 cc of pale yellow, clear liquid was present in the pelvis. There were no adhesions, and the peritoneum was smooth. (Smears from the liquid contained a few large mononuclear cells, and bacteria were not revealed by Gram or acid-fast stains.) The abdominal organs were in their normal positions. The appendix did not show any lesion. The mesenteric lymph nodes were greatly enlarged and seemed to be increased in number, but were of about normal consistency (fig 1). A cross-section showed only hyperplasia without evidence of tuberculosis.

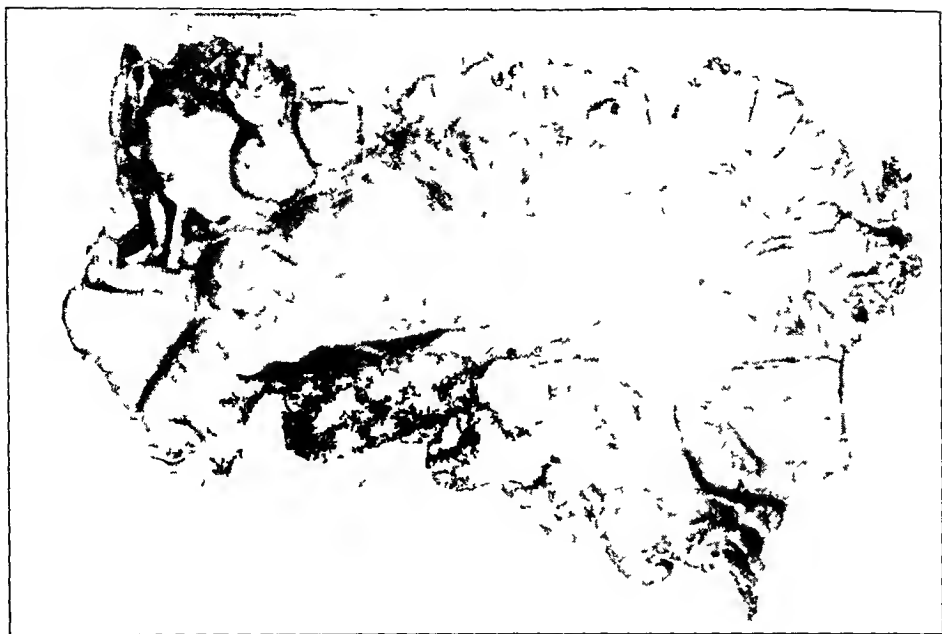


Fig 1—A mass of enlarged mesenteric lymph nodes, photograph after fixation



Fig 2—Cut surface of the left lung showing generalized fibrosis. The right lung is similar in appearance, photograph after fixation by Kaiserling's method

The pleural cavity contained about 30 cc of liquid on each side, and in it there were a few flocculent masses. Both pleural surfaces were covered with a thin layer of fibrin. There were no old adhesions. The pericardial cavity contained clear liquid, which was not increased in amount. The heart weighed 240 Gm. The pericardium, endocardium, myocardium and valves did not show any gross lesions. The measurements were within normal limits.

The weight of the lungs was right, 740 Gm, left, 600 Gm. Both lungs seemed to be completely consolidated. There was no place where crepitation could be made out. They were doughy and inelastic on palpation. The bronchi contained small amounts of mucoid exudate. A thin layer of fibrin covered most of the surfaces of both lungs. On section, the cut surface had a brick red, fleshy appear-

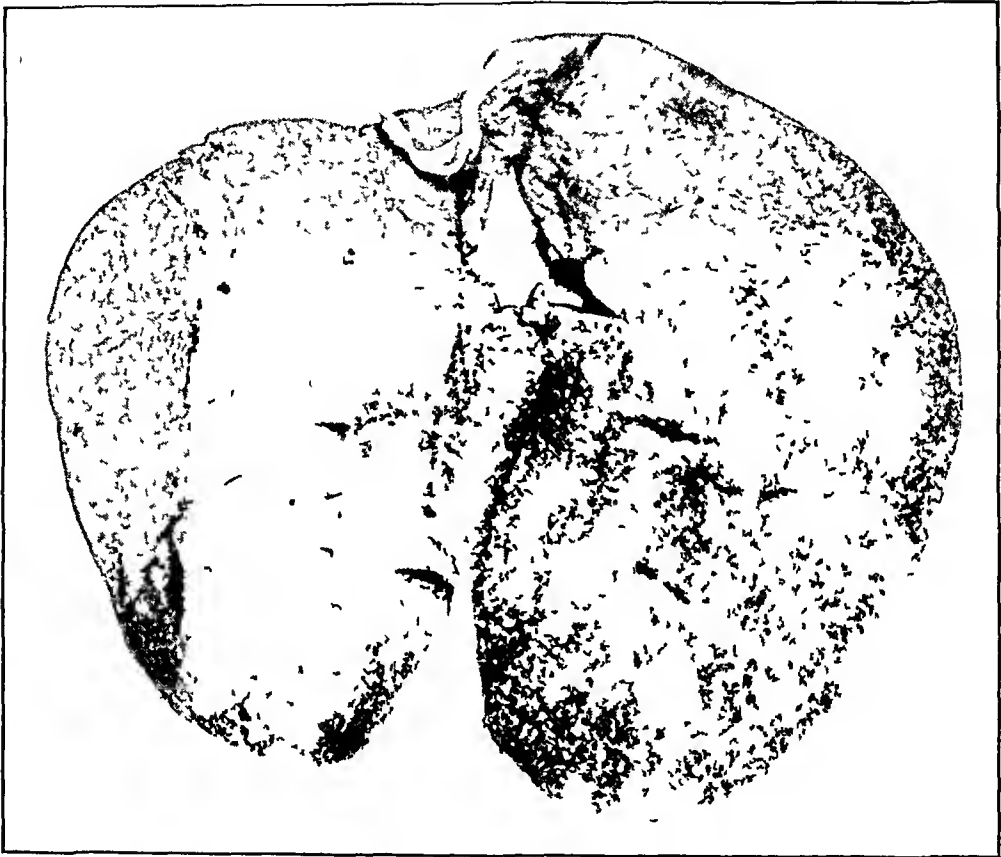


Fig 3—Photograph of spleen after Kaiserling fixation

ance, and was somewhat granular. The granules were pale, lighter in color than the background, but were not palpable, they did not seem to be tubercles. The cut surface of both lungs was uniform, having the same appearance throughout (fig 2). Large lesions, exudate or areas of caseation or of old fibrosis were not present. The lung was fairly dry, only a small amount of blood could be squeezed out, and no other liquid or pus.

The spleen weighed 380 Gm. It was greatly enlarged and brick red, the consistency was somewhat decreased over the normal. The capsule was of the usual thickness, smooth and not tense. The cut surface had a coarsely granular appearance, was grayish red, and had somewhat the appearance of the cut surface of the lung (fig 3). The granules were barely palpable, pale and firm, but not tuberculous. The pulp was not excessive, little could be scraped away with the knife.

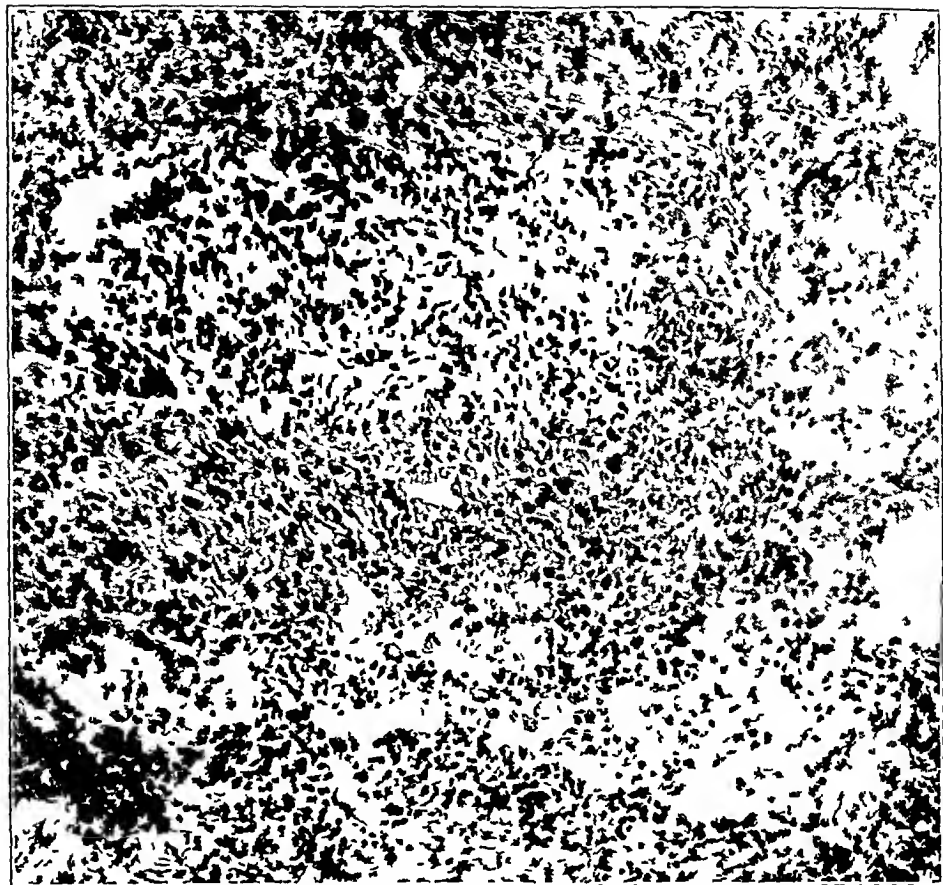


Fig 4—The appearance of the lung is that of a chronic progressing fibrosing condition rather than the organization of a previously acute inflammatory lesion
Giemsa stain, $\times 50$

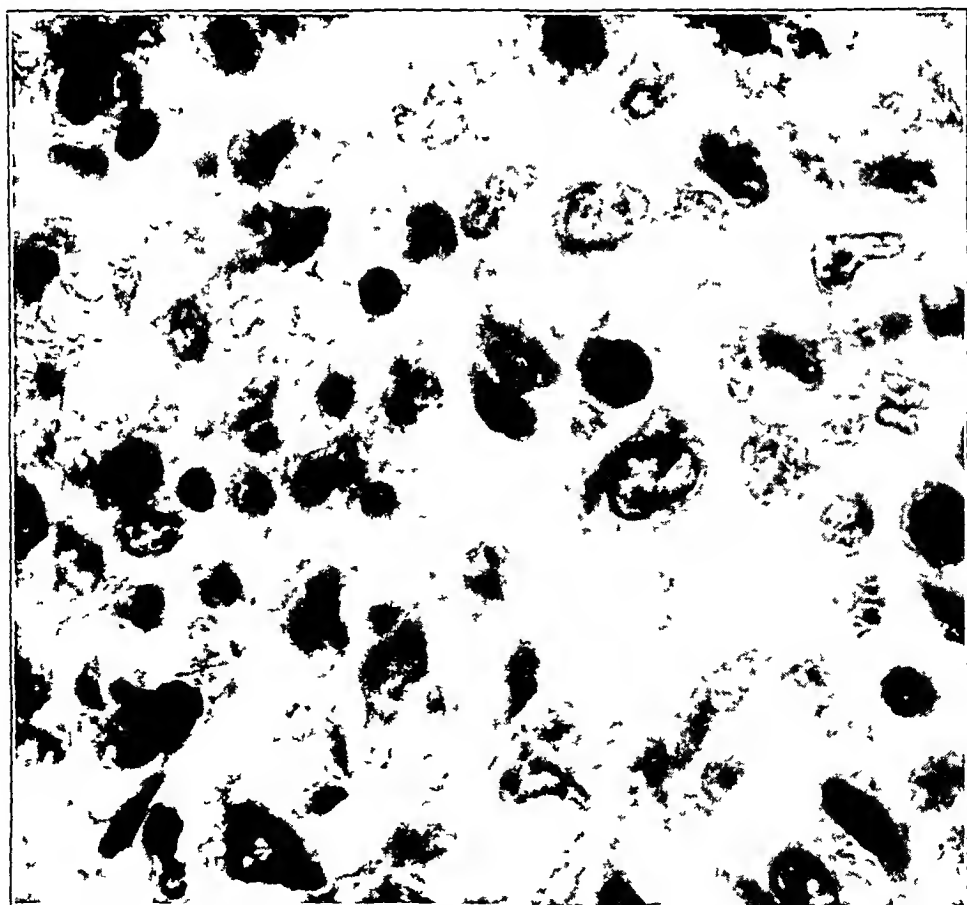


Fig 5—The types of cells present in the lung include endothelial cells forming capillaries, free endothelial leukocytes, fibroblasts and plasma cells
Giemsa stain, $\times 800$

The gastro-intestinal tract was opened from the esophagus to the anus but a lesion was not found. The pancreas itself was normal but around it, particularly along the splenic artery and at the head of the pancreas, there were numerous enlarged lymph nodes. The liver weighed 1,400 Gm. It seemed somewhat enlarged for the size of the child, but was normal in shape and in appearance. The cut surface was brownish gray, and showed the usual normal markings. The gall-bladder and ducts did not contain any lesions.

The weight of the kidneys was right, 140 Gm, left, 150 Gm. They were essentially the same in appearance. The capsules stripped easily, showing a smooth surface. The cortex was 0.6 cm in width, was regular and did not contain scars.

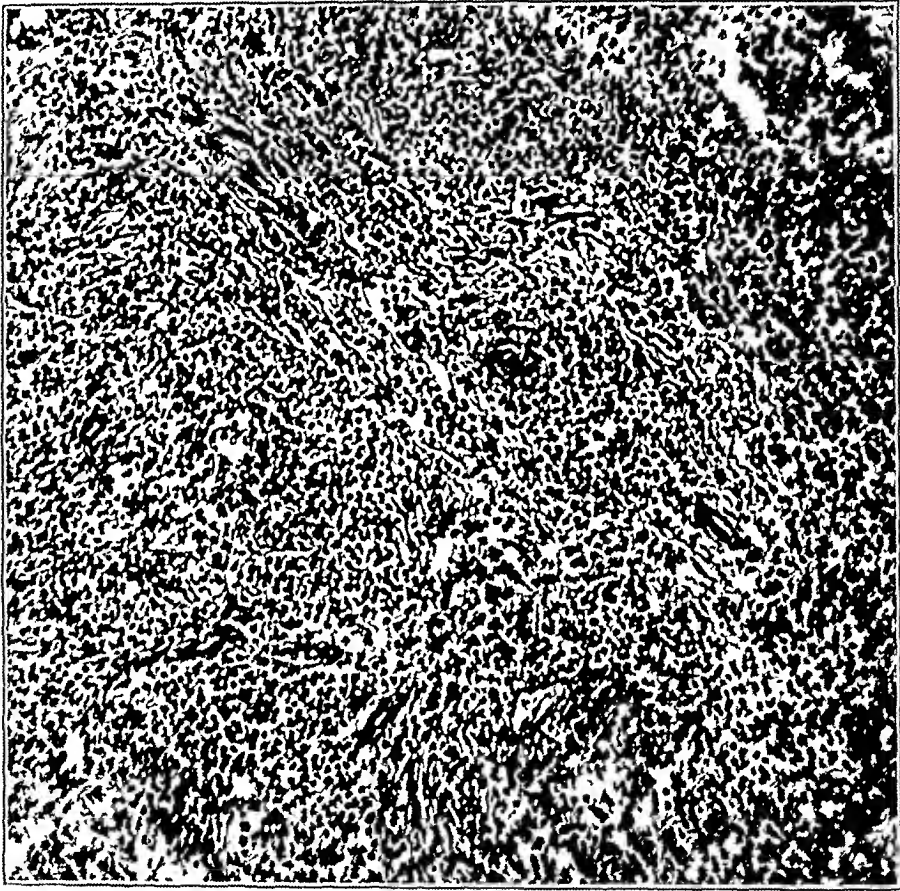


Fig 6—Fibroblastic proliferation in one of the splenic corpuscles. Hematoxylin and eosin stain, $\times 50$

The medulla and cortex showed moderate edema and congestion, but no other gross lesion.

There were no gross lesions in the suprarenals, bladder and genital organs. The testes were small and soft. The aorta was essentially normal. Around it the retroperitoneal glands were greatly enlarged up to the diaphragm. The bone marrow was red, although there were some small patches of fatty marrow. This was taken from the femur.

Several chains of lymph nodes were dissected out from both inguinal regions and from the neck. These were mostly soft and appeared to be hyperplastic without evidence of acute or chronic infection. One node from the inguinal region contained a mass of fibrous tissue in the center, and several others were rather firm and contained more fibrous tissue than usual. Caseation was not found in any

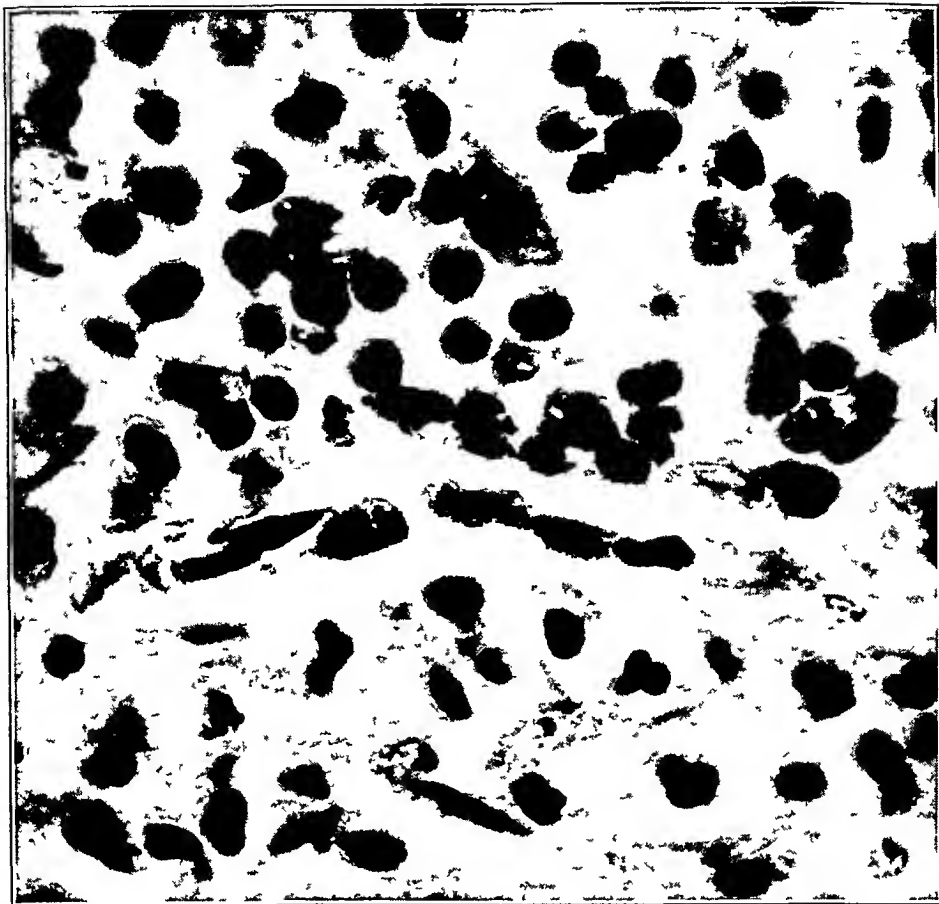


Fig 7—Endothelial proliferation and the character of the cells present in the spleen Giemsa stain, $\times 800$

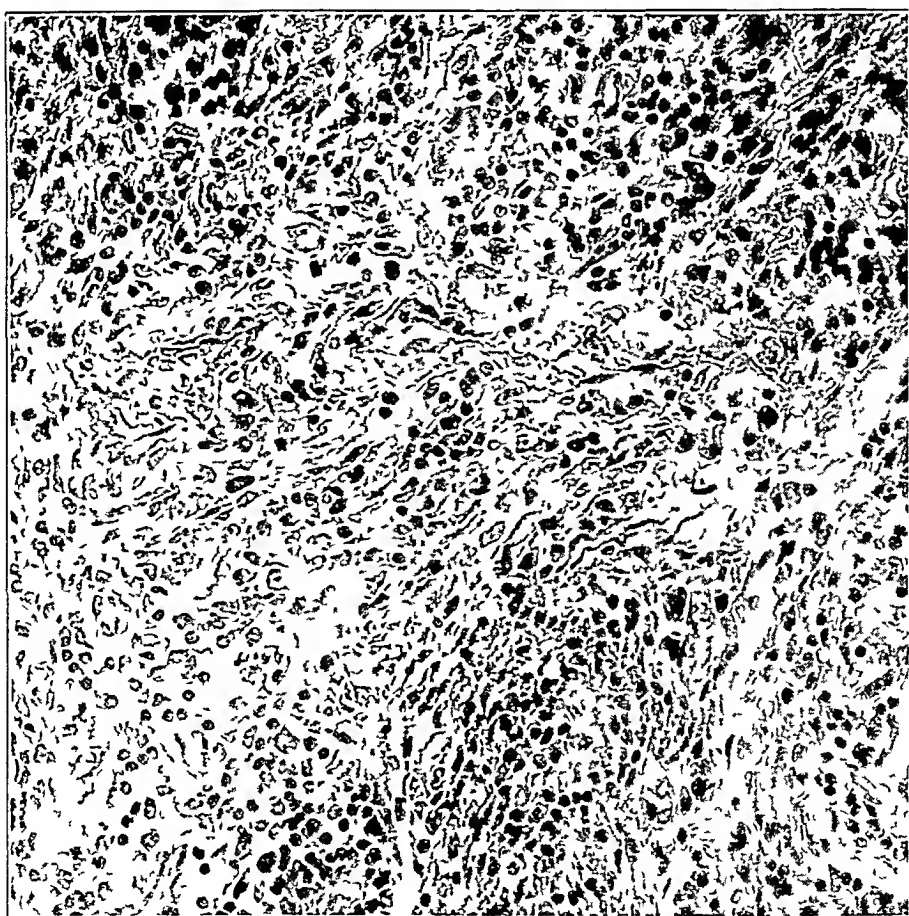


Fig 8—Proliferative lesion in the center of a lymphoid nodule Giemsa stain, $\times 50$

of the nodes, nor was there any other evidence of a localized lesion within the nodes. This seemed to be a generalized lymphatic hyperplasia or tumefaction, the nature of which was not apparent from gross examination alone.

Microscopic Examination—The pericardium and endocardium did not show any lesion. The muscle of the heart was well preserved. There was slight interstitial edema.

There was a peculiar organizing process throughout both lungs. Most of the alveolar walls were thickened with recent fibroblastic cells, and much of the lung substance had been replaced by fibrous tissue. The reaction was more interstitial



Fig 9—Mesenteric lymph node showing fibrosis of cortex, obstruction of peripheral sinuses, thickening and infiltration of the capsule and infiltration of the surrounding fat. Hematoxylin and eosin stain, $\times 20$.

and peribronchial than alveolar. The few alveolar spaces remaining contained a large cell exudate or were clear. A few contained small amounts of hyaline fibrin. The picture was not that of the usual organizing pneumonia (fig 4). The recently formed fibrous tissue did not follow the course of strands of fibrin in the usual manner. Many alveoli were plugged or obliterated by connective tissue and newly formed capillaries, but these plugs were continuous with and inseparable from the fibroblastic changes in the alveolar walls. Around the bronchi and bronchioles there were thick collars of fibrous tissue, and the alveoli adjacent to these seemed to be affected more than those at a distance.

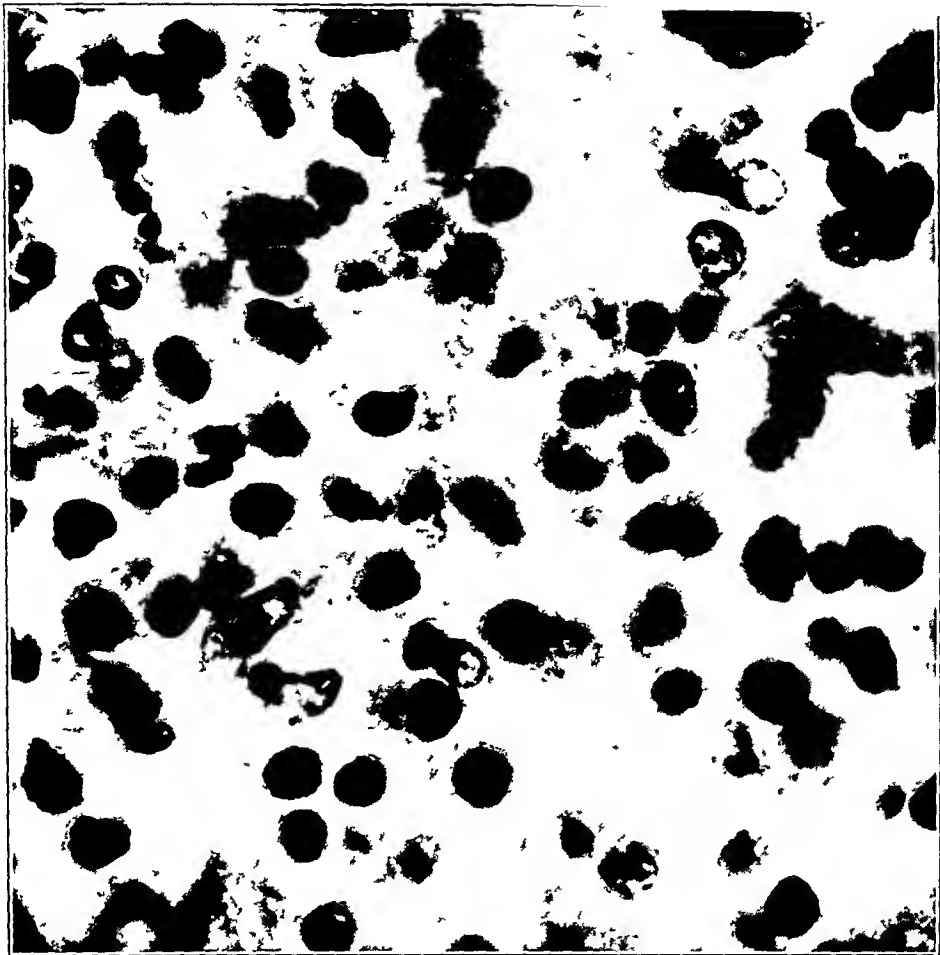


Fig 10—The character of the cells in the lymph nodes Giemsa stain, $\times 800$

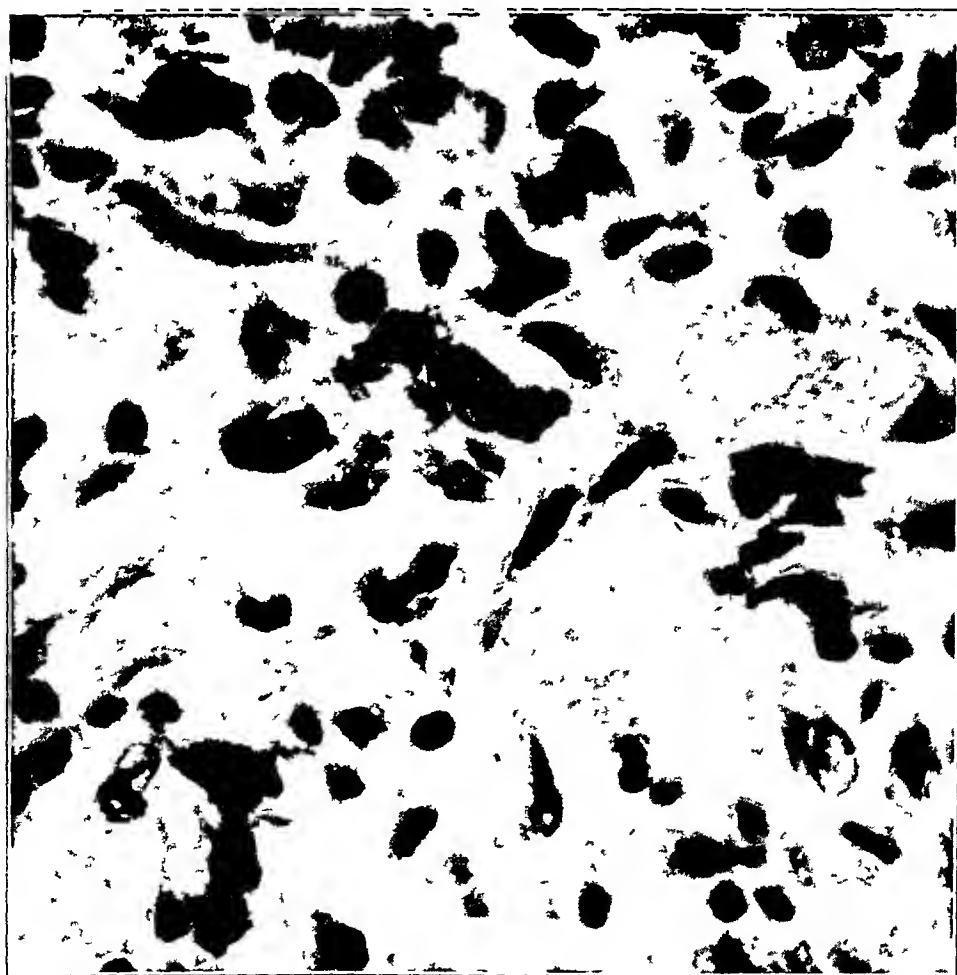


Fig 11—Endothelial and fibroblastic proliferation and capillary formation in lymph node Phosphotungstic acid hematoxylin stain, $\times 800$

Embedded in, and intimately intermingled with, the fibroblasts were many endothelial cells. Some of these were forming capillaries, which were numerous, others were lying free in the tissue (fig 5). A rare mitotic figure was seen among these cells. Other cells included numerous plasma cells and rare polymorphonuclear cells. Some of the bronchi contained small amounts of polymorphonuclear and mononuclear cell exudate.

Phosphotungstic acid hematoxylin and Giemsa's stain were used to study the intercellular substance and the cell types. These showed only more clearly the fibroblastic and endothelial cell proliferation, and emphasized the number of plasma cells present. Definite organisms could not be seen in the Giemsa prepara-

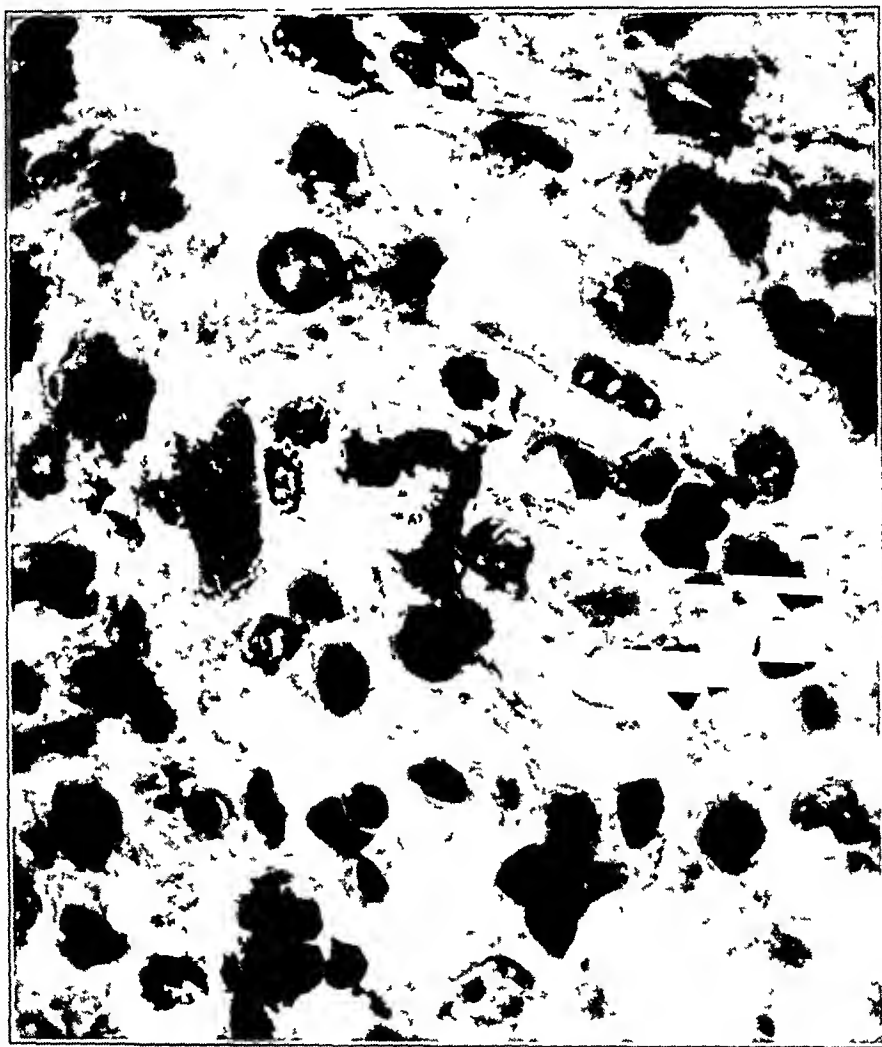


Fig 12—Cellular portion of lymph node resembling Hodgkin's disease, for comparison with figure 13. Giemsa stain, $\times 800$.

tions, and bacilli were not found in sections stained for acid-fast organisms. Levaditi preparations did not show any spirochetes.

The pleura contained a thin layer of fibrin on the surface embedded in which were small numbers of polymorphonuclear cells and lymphocytes.

The spleen was cellular throughout, containing little blood. A fibrosing process was present which affected particularly the splenic corpuscles (fig 6). These were present in increased numbers and prominence and most of them contained a proliferative lesion around the central arteriole. Here there was active fibroblastic and endothelial cell proliferation, intermingled with normal appearing

lymphocytes and a scattering of plasma cells and polymorphonuclear neutrophils (fig 7). A few eosinophils were present, and infrequent, large, irregularly shaped cells with purple cytoplasm (hematoxylin and eosin) and large, irregularly shaped nuclei with reticulated chromatin (identical with Dorothy Reed cells) were also found. This same process was present in less degree throughout the spleen, obscuring the sinuses, although in general, the normal architecture was not greatly altered. The capillary endothelium was prominent, and rare mitotic figures were present in these cells. The splenic capsule was slightly or not at all thickened. Organisms could not be found in Giemsa and Levaditi preparations.

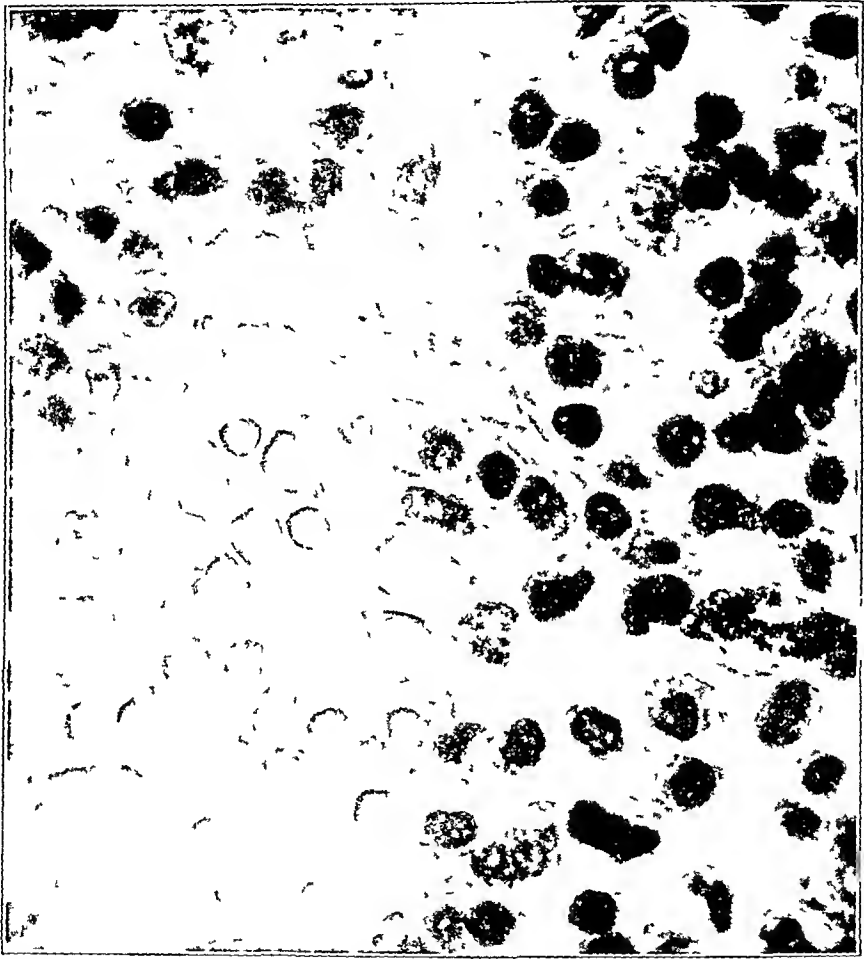


Fig 13—Section of cervical lymph node from a typical case of Hodgkin's disease, for comparison with figure 12. Hematoxylin and eosin stain, $\times 800$.

The parenchyma of the liver appeared to be normal. There was no increase in the fibrous tissue, and no cellular infiltration. The bile ducts were normal. The pancreas and suprarenals did not show any lesions. The kidneys were only moderately congested. Recent or old lesions were not seen. There was no cellular infiltration. Spermatogenesis was not active. Spermatozoa were not present in the testis, and there was no proliferation of spermatids. The tubules were separated by wide bands of stroma, as were also the tubules of the epididymis. Interstitial cells seemed to be present in the usual number. The bladder and prostate did not show any lesions.

Nearly all the nodes contained a granulomatous lesion in which there was more or less fibrosis (fig 8). Few if any lymphoid nodules were present, and germinal centers were rare. In most of the glands the peripheral sinuses could not be seen, they were either collapsed or filled with fibrous tissue and cells. Many of the medullary sinuses were also obscured by an overgrowth of a similar nature, though some were recognizable. The capsules, as a rule, delimited the gland sharply, but one section showed two nodes with united capsules due to cellular and fibroblastic infiltration. A large mesenteric node showed cellular infiltration, not only into the thickened capsule, but also into the surrounding fat (fig 9). The nodes showed fibroblastic-endothelial cell proliferation throughout, but in places

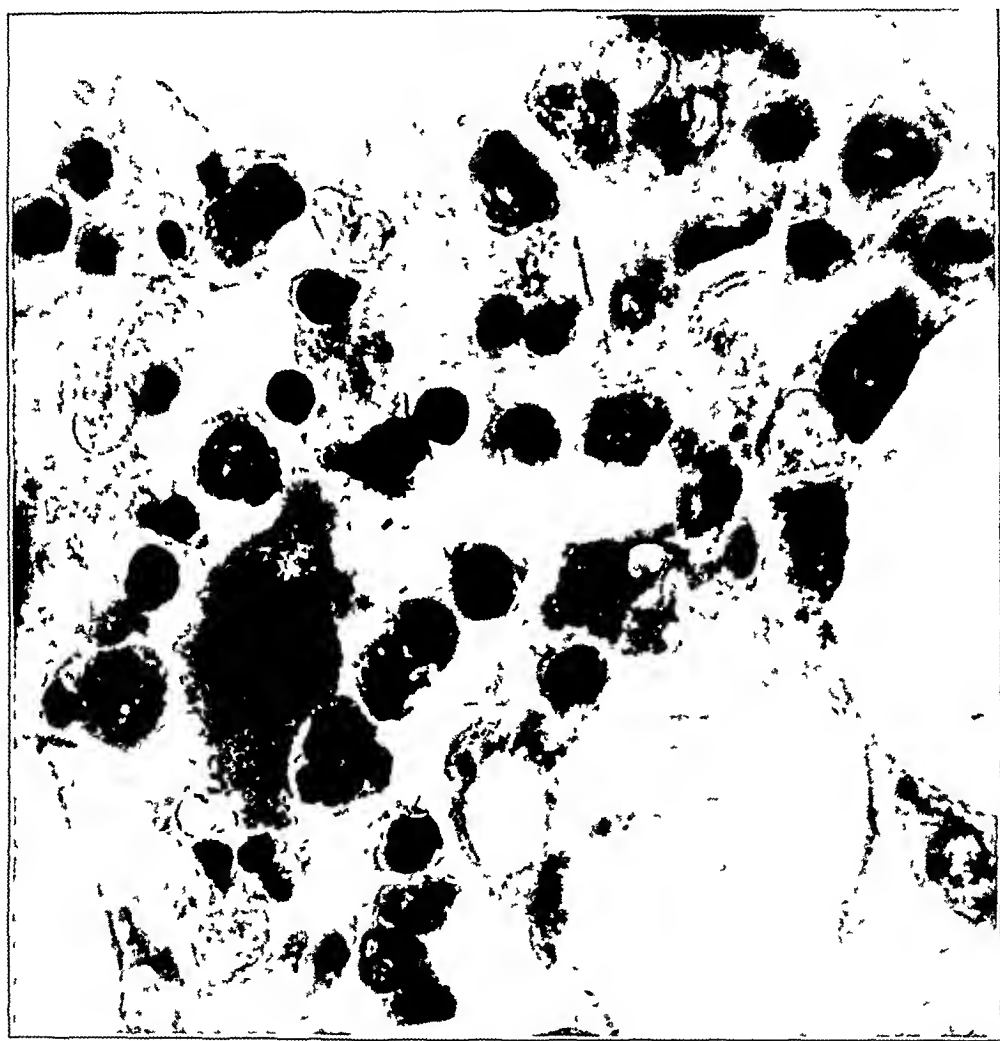


Fig 14—Endothelial (or reticular) hyperplasia, showing the predominant cell types in the bone marrow. Giemsa stain, $\times 800$.

there was condensation of the connective tissue, mostly in what appeared to be the centers of obliterated lymphoid nodules. The cells present included endothelial cells, plasma cells, lymphocytes and rare polymorphonuclear neutrophils (fig 10). Eosinophils were extremely rare, only one or two were found in eight sections. Large, irregularly shaped cells with large nuclei, occasionally two nuclei, were infrequent, but a few were seen in each node. These were identical with the tumor cells (Dorothy Reed cells) of Hodgkin's disease. Mitotic figures were not numerous, but were seen in endothelial cells and in other undifferentiated cells.

(figs 11, 12, 13) The exact nature of the lesion could not be determined. It resembled Hodgkin's disease, but in general was more of a chronic inflammatory lesion.

There was moderate diffuse hyperplasia of the bone marrow. Most of the fat cells were separated by distended sinusoids filled with cells. These cells were mostly of one type—fairly large cells with purple cytoplasm and round nuclei (fig 14). In most cells the chromatin was abundant, but scattered, forming no particular pattern within the nucleus. Cells of similar appearance were seen attached to the walls of capillaries and sinuses. Myelocytes were rare, and no nucleated red cells were seen. Megakaryocytes were present in normal or in slightly increased numbers. Pigment was not present, and organisms were not seen in Giemsa preparations.

SUMMARY

The case of a boy with a chronic progressive condition of the lungs, lymph nodes and spleen which lasted for thirty days, and which ended with massive consolidation of the lungs is recorded. At autopsy there was widespread enlargement of the lymph node, a diffuse fibrosis of both lungs and a large somewhat granular spleen. The bone marrow was moderately hyperplastic. Histologically, there were fibrosis, endothelial cell proliferation and cellular infiltration of the lymph nodes of a definitely inflammatory character, but in some places closely resembling the sclerosing lymphosarcoma of Hodgkins' disease. The spleen and lungs showed similar pictures, the histology of the lung being that of a chronic progressing fibrosis rather than the organization of a previous acute exudative lesion. The causative organism was not found.

EXPERIMENTAL UREMIA-UREMIC ENTERITIS^{*}

M H STREICHER, M D
CHICAGO

The purpose of this experimental study was (a) to produce a disturbance in a dog that parallels the clinical features of uremia, (b) to study the effects of such a disturbance on the gastro-intestinal canal, and (c) to arrive at a possible explanation of uremia on a chemical basis. As urea is the principal constituent of the urine, I naturally employed this metabolite as the uremia-producing substance.

Visceral disturbances in uremia are frequently so pronounced that the writers of the nineteenth century often referred to this condition as visceral uremia. The literature on this subject is profuse and at wide variance. I, therefore, will consider only a few references which deal directly with the problem.

REVIEW OF THE LITERATURE

The chemical theory of Wilson in 1833 ascribes uremia as due to the retention of urea in the blood stream. This theory met with considerable opposition and was primarily contested by Frerichs (1852), Herker (1898), Ritter (1880) and Bouchard (1887).

In 1860, the anatomic theory became temporarily popular through the researches of Traube, who believed that uremia was caused by edema of the brain and consequent disturbances in circulation.

In 1889, Brown-Sequard published his theory on internal secretion and described the causation of uremia as due to failure of kidney secretion.

Since 1889, little advance had been made on the subject until 1912, when Folin and his co-workers¹ introduced accurate methods for chemical analysis of the blood and the urine.

Considerable data have been accumulated by Marshall,² Van Slyke,³ Myers and Fine,⁴ Denis, Austin and Farr,⁵ McLean and Selling,⁶

^{*} From the Department of Medicine, Research and Educational Hospital, University of Illinois College of Medicine.

1 Folin and Farmer. *J Biol Chem* **11**:493, 1912. Folin. *ibid* **11** 507, 1912. Folin and Macallum. *ibid* **11** 523, 1912. Folin and Denis. *ibid* **11**:527, 1912.

2 Marshall. *J Biol Chem* **14** 283, 1913, *ibid* **15**:487, 1913, *ibid* **15**:495, 1913.

3 Van Slyke and Cullen. *J Biol Chem* **19** 211, 1914, *ibid* **24**:117, 1916.

4 Myers and Fine. *J Biol Chem* **20** 391, 1915.

5 Farr and Austin. *J Exper Med* **18** 228, 1913.

6 McLean and Selling. *J Biol Chem* **19** 31, 1914.

Schwartz and McGill⁷ and Chace and Myers⁸ on the retention of non-protein nitrogen, urea nitrogen and uric acid. It is interesting to note that Vanquelin and Segales, in 1822, were the first to record intravenous injections of urea in animals. In 1858, Hammond interfered with the kidneys while making injections of urea, and found that the injections were fatal. In some animals, one ureter was ligated and it was found that after a short time the remaining functioning kidney would take care of as much urea as both kidneys previous to the operation, indicating a high margin of safety. In 1920, Wells⁹ was inclined to the view that uremia was caused by the retention of the known nitrogenous substances in the blood, and emphasized especially the importance of the time element.

Experiments with the Woodyatt machine to determine the effects of prolonged intravenous injections of the various purified urinary constituents were recommended as being highly essential for further progress. An interesting set of experiments was carried out by Andrews¹⁰ (1927), in which a chemical picture simulating uremia was reproduced by intravenous injection of a 5 per cent saline solution.

MATERIALS AND METHODS

Dogs were repeatedly injected with from 10 to 20 per cent urea (Merck) solution (at body temperature) intravenously, 200 cc was given daily for three days at the rate of from 1 to 5 cc a minute. Dietary restrictions were not used except in one group of controls.

General anesthesia was necessary only in some instances. The injections were made by means of a Woodyatt pump into the femoral vein. No evidence of hemolysis was present. The animals were kept in individual cages and were carefully controlled, samples of the heart's blood, feces and urine of each animal were collected at twenty-four hour intervals for chemical analysis. Necropsy was performed on all the dogs soon after the death. The viscera were examined and sections were made for histologic study.

One ureter had been ligated in many instances.

EXPERIMENTAL WORK

In about 40 per cent of the dogs, a picture similar to that of uremic coma, the so-called "Kussmaul picture," was produced after a single injection of 200 cc of 10 or 20 per cent solution of urea, and in practically 100 per cent of the animals, coma was invariably produced after the second or third injection.

7 Schwartz and McGill. Blood Urea, *Arch Int Med* **17** 42 (Jan) 1916.

8 Chace, A. F., and Myers, V. C. The Value of Recent Laboratory Tests in the Diagnosis and Treatment of Nephritis, *J A M A* **67** 929 (Sept 23) 1916.

9 Wells. Chemical Pathology, Philadelphia, W. B. Saunders Company, 1920.

10 Andrews, Edmund. Experimental Uremia, *Arch Int Med* **40** 548 (Oct) 1927.

A representative example of each group of experiments is included in the following reports

The experiments on dog 1 represent a group in which the right ureter had been ligated and food has been allowed

Dog 1—A female dog, weighing 15.6 Kg, received 200 cc of 10 per cent urea solution daily for three days. Salivation was noticed after 100 cc of the solution was injected. Vomiting occurred after 200 cc was injected, and dyspnea and restlessness after the injection of 300 cc.

An injection of 400 cc of the solution produced generalized tremors and 500 cc, convulsions.

Bloody diarrhea, retraction of the head and neck, unconsciousness and death followed the injection of 600 cc of the solution of urea.

The chemical analysis of this animal is included in the group represented by table 1.

The necropsy report revealed that the entire gastro-intestinal canal was markedly injected and hyperemic, there was no evidence of ulcerations. The left kidney was apparently normal in gross. The right kidney was distended with fluid and the medullary substance disappeared entirely. The lungs showed marked hyperemia. The liver was dark and full of blood.

Histologic examination showed marked enteritis of the gastro-intestinal canal. The liver was congested, and there was marked engorgement. Cloudy swelling of epithelium, and hyperemia were noted in the kidney. Hyperemia was observed in the lung. No other changes were noted.

Dog 2 is representative of a group in which the right ureter had been ligated, but no food given.

Dog 2—A female dog, weighing 14.3 Kg, received 200 cc of a 10 per cent solution of urea daily for three days. The animal followed the same course as dog 1. The chemical analysis is demonstrated by table 2. The necropsy observations and results of the histologic examination were identical with those made on dog 1.

This set of experiments was instituted to determine what effect, if any, limitation of food would have on the chemical analysis of the excretory products.

Dog 3 is representative of a group in which the right ureter had been ligated and food was given, and dog 4 of the group in which both ureters remained intact, and food given.

Dog 3—A female, weighing 16.5 Kg, received 200 cc of a 20 per cent solution daily for three days (table 3).

Dog 4—A female, weighing 16.2 Kg, received 200 cc of a 20 per cent solution daily for three days (table 4).

RESULTS

The chemical observations made during the various sets of experiments are shown in figures 1 and 2.

TABLE 1—*Chemical Analysis of Intravenous Injection of Urea Solution as in Dog 1**

	Before Injection			24 Hours After Injection			48 Hours After Injection			72 Hours After Injection			Remarks
	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	
Output	600 cc		21 Gm	290 cc		54 Gm	1,900 cc		7 Gm	1,250 cc		18 Gm	Right ureter li
Total nitrogen	3.2 Gm		5.1 Gm	4.9 Gm		2.4 Gm	13.0 Gm		0.3 Gm	9.5 Gm		1.1 Gm	gated, average
Ammonia nitrogen	0.46 Gm		0.01 Gm	0.19 Gm		0.13 Gm	1.9 Gm		0.02 Gm	2.4 Gm		0.09 Gm	Weight of dog
Urea nitrogen	0.4 Gm	24 mg	0.03 Gm	3.2 Gm	38 mg	0.0 Gm	10.2 Gm	35 mg	0.1 Gm	6.4 Gm	22 mg	0.02 Gm	16 Kg., (female,
Albumin	—			+			+			+			food given)
Carbon dioxide		51.2 cc			40.1 cc			36.3 cc			30.4 cc		series of 6 dogs
Chlorides		389 mg			425 mg			501 mg			528 mg		convulsions,
Calcium		6.3 mg			17.4 mg			10.1 mg			8.2 mg		Cheyne Stokes
Potassium		2.1 mg			22 mg			19.0 mg			21.0 mg		breathing, diar
Index of refraction		58			54			51			51		then coma,
													death

* Two hundred cubic centimeters of 10 per cent solution was given daily for three days, rate of injection, 5 cc a minute

TABLE 2—*Chemical Analysis of Intravenous Injection of Urea Solution as in Dog 2**

	Before Injection			24 Hours After Injection			48 Hours After Injection			72 Hours After Injection			Remarks
	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	
Output	700 cc		28 Gm	500 cc		32 Gm	500 cc		18.3 Gm	600 cc		14 Gm	Right ureter li
Total nitrogen	3.4 Gm		6.0 Gm	7.12 Gm		8.1 Gm	4.6 Gm		3.2 Gm	6.1 Gm		2.3 Gm	gated, average
Ammonia nitrogen	0.38 Gm		0.05 Gm	0.14 Gm		0.14 Gm	0.21 Gm		0.109 Gm	1.2 Gm		0.07 Gm	Weight of dog
Urea nitrogen	0.48 Gm	18 mg	0.04 Gm	4.8 Gm	96 mg	0.0 Gm	3.6 Gm	45 mg	0 Gm	3.1 Gm	21 mg	0.03 Gm	15 Kg., (female,
Albumin	—			+			+			+			no food given),
Carbon dioxide		45.7 cc			44.7 cc			30.5 cc			30.4 cc		series of 6 dogs,
Chlorides		440 mg			501 mg			711 mg			680 mg		convulsions,
Calcium		7.2 mg			21.3 mg			19.1 mg			9.6 mg		vomiting,
Potassium		21.9 mg			17.4 mg			16.4 mg			18.4 mg		Cheyne Stokes
Index of refraction		58			54			50			51		breathing, diar
													rhea, coma,
													death

* Two hundred cubic centimeters of 10 per cent solution was given daily for three days, rate of injection, 5 cc a minute

TABLE 3—Chemical Analysis of Intravenous Injection of Urea Solution as in Dog 3 *

Output	Before Injection			24 Hours After Injection			48 Hours After Injection			72 Hours After Injection			Remarks
	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	
Total nitrogen	700 cc		31 Gm	200 cc		69 Gm	480 cc		80 Gm	650 cc		68 Gm	Remarks
Ammonia nitrogen	47 Gm		39 Gm	59 Gm		21 Gm	139 Gm		18 Gm	119 Gm		14 Gm	Right ureter il-
Urea nitrogen	04 Gm		002 Gm	05 Gm		013 Gm	038 Gm		035 Gm	16 Gm		034 Gm	lated, average
Albumin	038 Gm	19 mg	004 Gm	45 Gm	42 mg	006 Gm	104 Gm	83 mg	01 Gm	71 Gm	76 mg	008 Gm	weight of dog
Carbon dioxide	—			+			+			+			17 kg, female,
Chlorides													food given,
Calcium		52.4 cc			46.1 cc			40.8 cc			32.1 cc		series of 15
Potassium		402 mg			552 mg			533 mg			492 mg		dogs, convul-
Index of refraction		82 mg			193 mg			244 mg			113 mg		sions, vomiting
		202 mg			147 mg			131 mg			234 mg		diarrhea, in-
		50			51			45			50		creased respira-
													tion comm
													death

* Two hundred cubic centimeters of 20 per cent solution was given daily for three days, rate of injection, 5 cc a minute

TABLE 4—Experimental Uremia Chemical Analysis of Intravenous Injection of Urea Solution as in Dog 4

Output	Before Injection			24 Hours After Injection			48 Hours After Injection			72 Hours After Injection			Remarks
	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	Urine	Blood	Feces	
Total nitrogen	770 cc		22 Gm	600 cc		11 Gm	800 cc		16 Gm	750 cc		9 Gm	Ureter not il-
Ammonia nitrogen	11 Gm		40 Gm	68 Gm		18 Gm	228 Gm		23 Gm	165 Gm		11 Gm	lated, average
Urea nitrogen	03 Gm		003 Gm	06 Gm		01 Gm	048 Gm		02 Gm	06 Gm		01 Gm	weight of dog
Albumin	01 Gm	18 mg	005 Gm	44 Gm	49 mg	002 Gm	216 Gm	129 mg	01 Gm	12 Gm	118 mL	0 Gm	17 kg, female,
Carbon dioxide	—			+			+			+			food given,
Chlorides													series of 9 dogs,
Calcium		70.8 cc			41 cc			37 cc			32 cc		convulsions,
Potassium		118 mg			531 mg			794 mg			673 mg		vomiting,
Index of refraction		81 mg			154 mg			1859 mg			162 mg		Cheyne Stokes
		20 mg			174 mg			14 mg			131 mg		breathing,
		54			51			51			18		diarrhea comm,
													death

* Two hundred cubic centimeters of 20 per cent solution was given daily for three days, rate of injection, 5 cc a minute

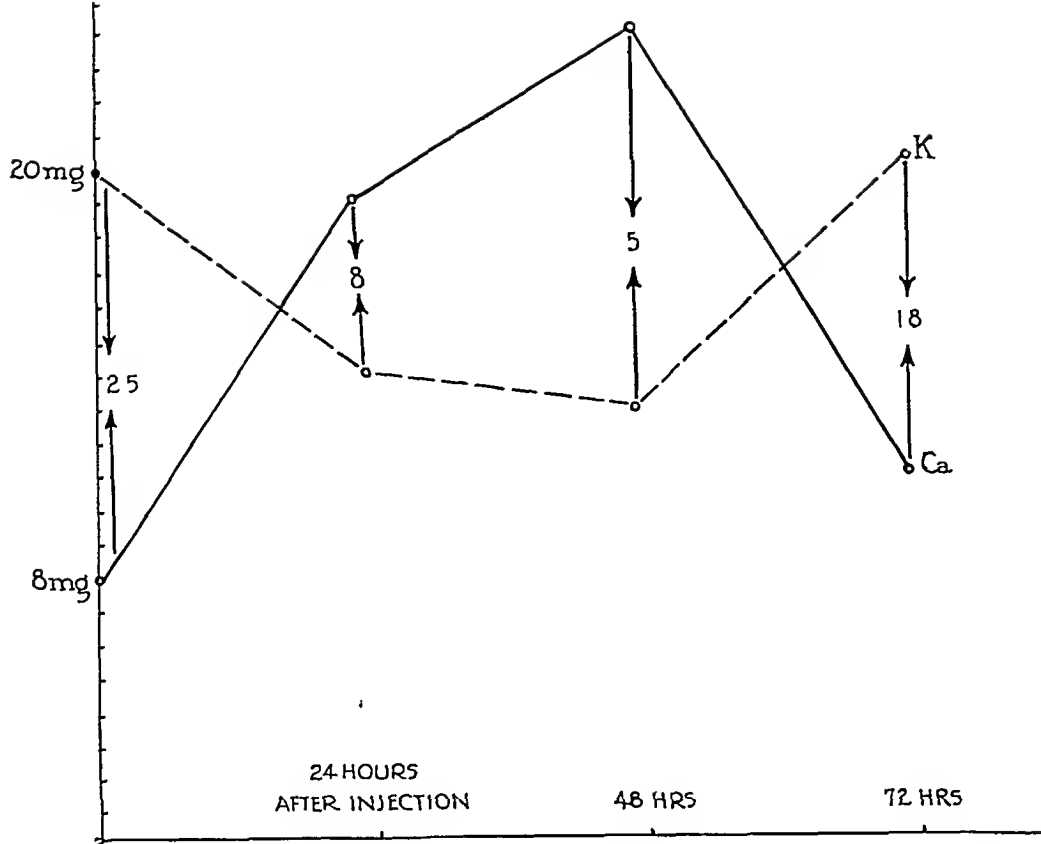


Fig 1—Experimental uremia, showing the calcium-potassium ratio In this case the right ureter was ligated

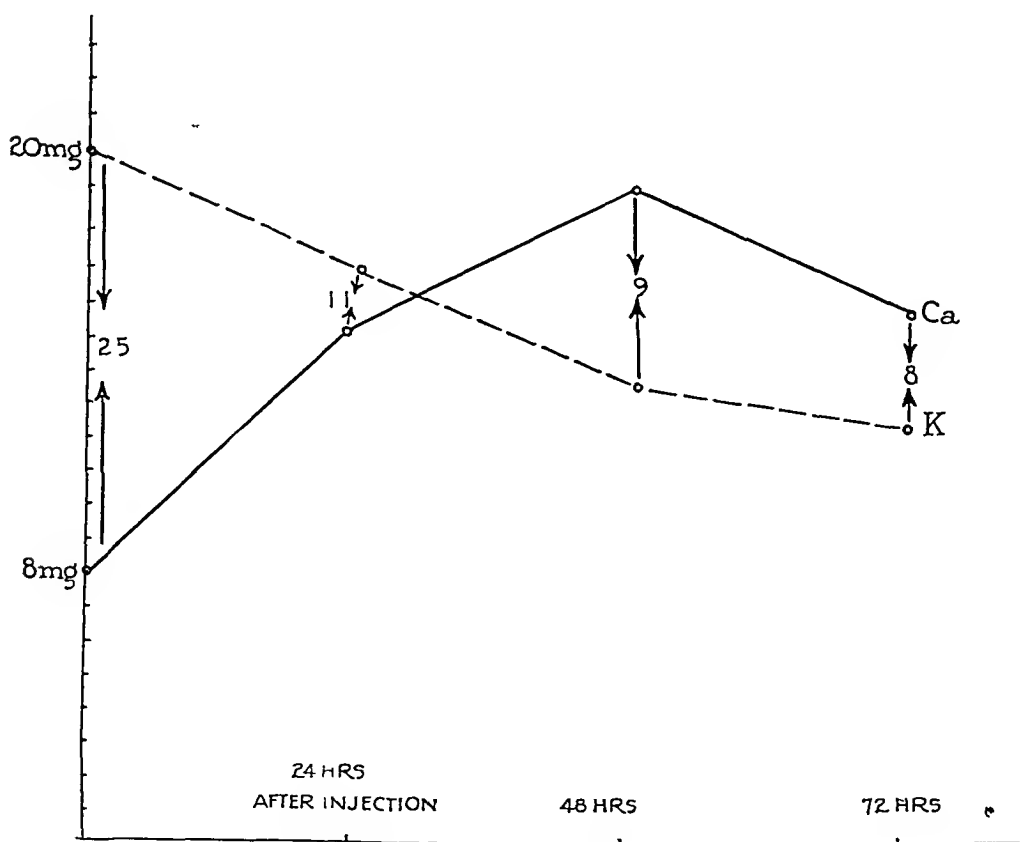


Fig 2—Experimental uremia, showing the calcium-potassium ratio In this case the ureter was not ligated

The outstanding features of these experiments are as follows (a) a progressive acidosis demonstrated by a marked fall in carbon dioxide content, (b) a marked fall in proteins in the blood is evident in the decrease of the refractometric index, (c) marked rise in urine chlorides, (d) disturbance in the calcium—potassium ratio (the ratio approaching 1 or 1 plus), (e) marked increase in urea in the blood, (f) a positive (++) test for albumin in urine is constant

Table 4 gives the chemical analysis of nine dogs in which the ureter had not been ligated. It is of interest to point out the marked parallelism of these results as compared with results in all other animals in which the ureter had been ligated.

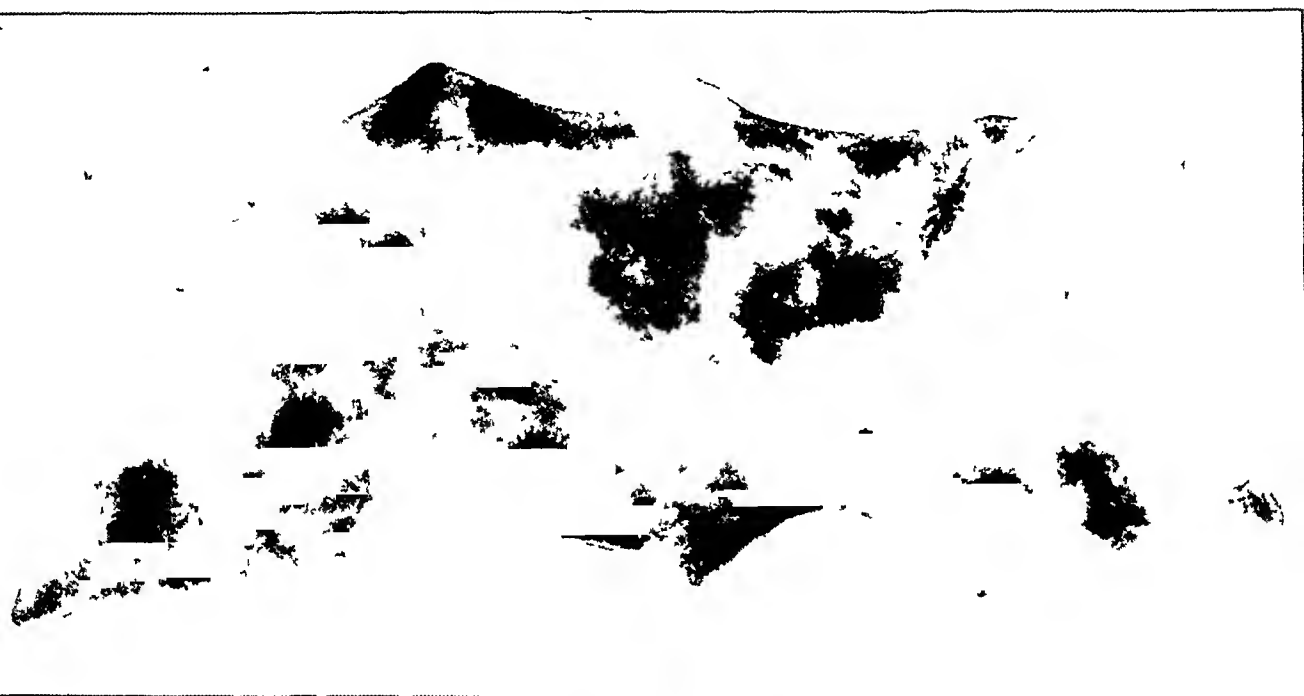


Fig. 3—Pathologic changes in the intestine—a marked enteritis and congestion. There is no evidence of ulceration.

The pathologic observations made from the experiments are shown in figures 3, 4, 5 and 6.

No other observations of consequence were found and, therefore, other examinations of the tissues are not reported.

COMMENT

Urea—On careful analysis of the output of urea in the form of ammonia nitrogen and urea nitrogen, it is evident that only about 25 per cent is recovered in the urine and feces, therefore, the concentration of urea in the blood was studied carefully. Two hundred cubic centimeters of a 20 per cent solution of urea was injected intravenously

into a dog (female) for three days and frequent chemical determinations were made for urea in the heart's blood (fig 7)

It is clearly demonstrated that the urea in the blood is markedly elevated after a single injection (175 mg in thirty minutes), and that the peak reaches 400 mg after the second injection and 700 mg after the third injection

Calcium-Potassium Ratio—The most striking features in the chemical studies were the profound changes in the mineral salt balance,

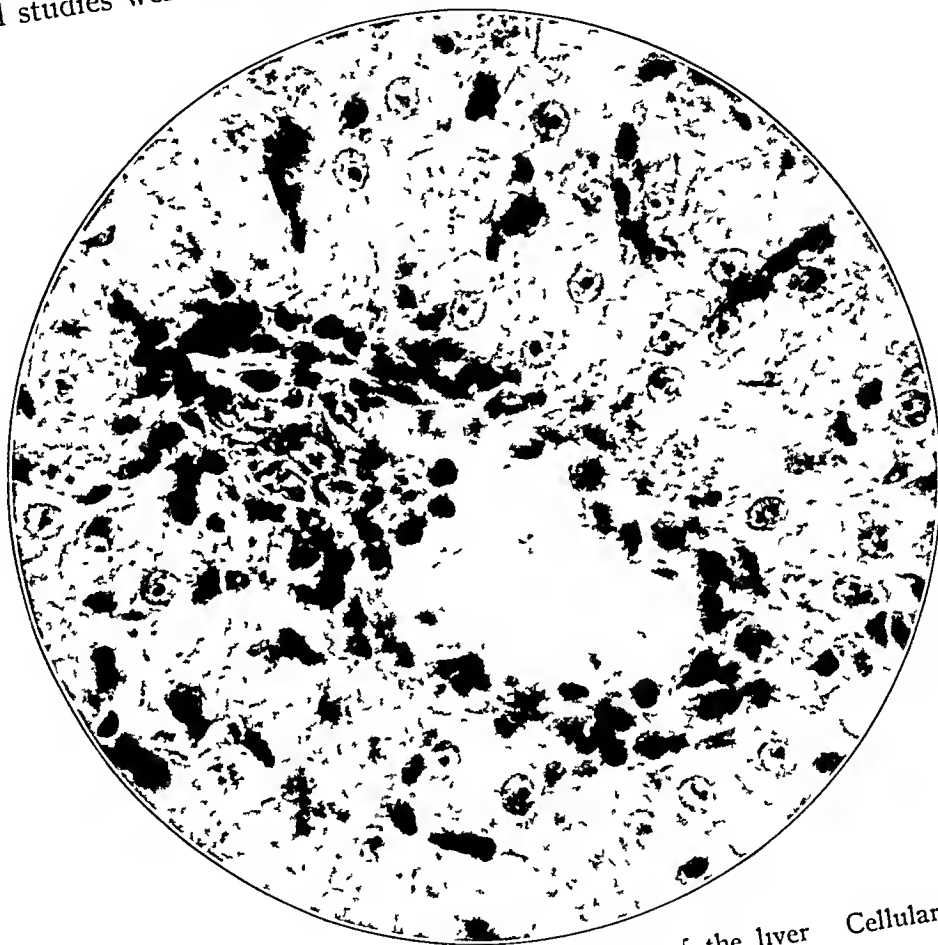


Fig 4—Marked engorgement and congestion of the liver Cellular changes are not observed

brought about by the injections of urea An almost unprecedented rise in the calcium of the blood takes place, accompanied by a correspondingly profound fall in the potassium So marked are these changes that the potassium-calcium ratio falls from a normal about 2.5 to levels far below 1 (figs 1 and 2)

It is striking that these changes in permeability correspond exactly with those reported in Andrews' "Experimental Uremia" which were produced by solutions of sodium chloride One is led to believe that the

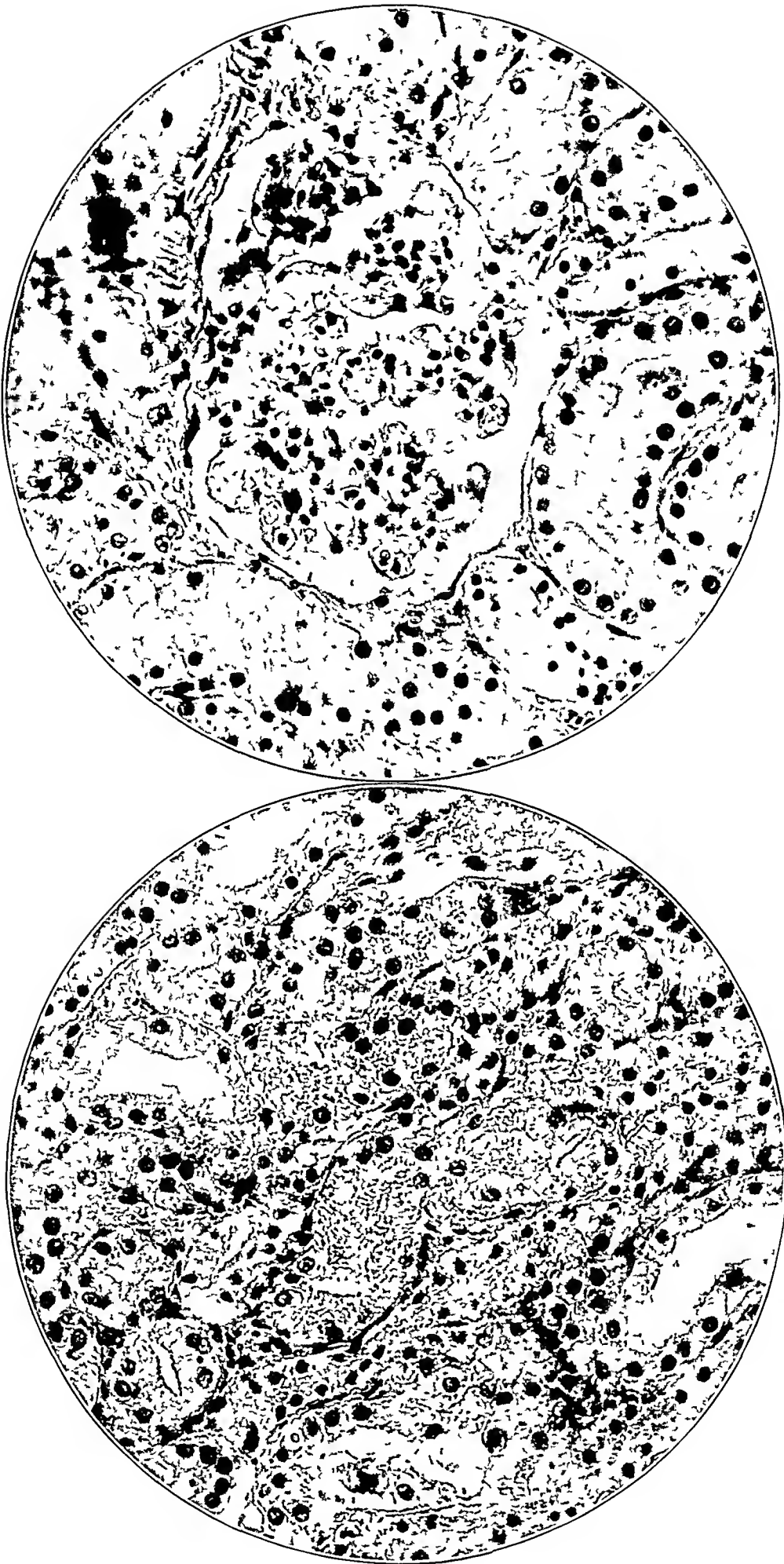


Fig 5—Photomicrographs of a kidney showing normal glomerulus and several convoluted tubules in which marked obstruction of the lumen is evident. Considerable hyperemia and marked cloudy swelling of the epithelium may be noted.

injections of urea bring about disturbances of the osmotic equilibrium under conditions of acidosis much the same as the sodium chloride will, and that the mechanism of production of the uremic symptoms is the same, that is, that owing to changes in cell permeability, toxic nitrogenous products are allowed to leak into the circulation

Although slight histologic changes in the liver were noted in my experiments, the urine from two of the animals was studied immunologically by Dr Thomas and shown to react in high dilutions to liver protein

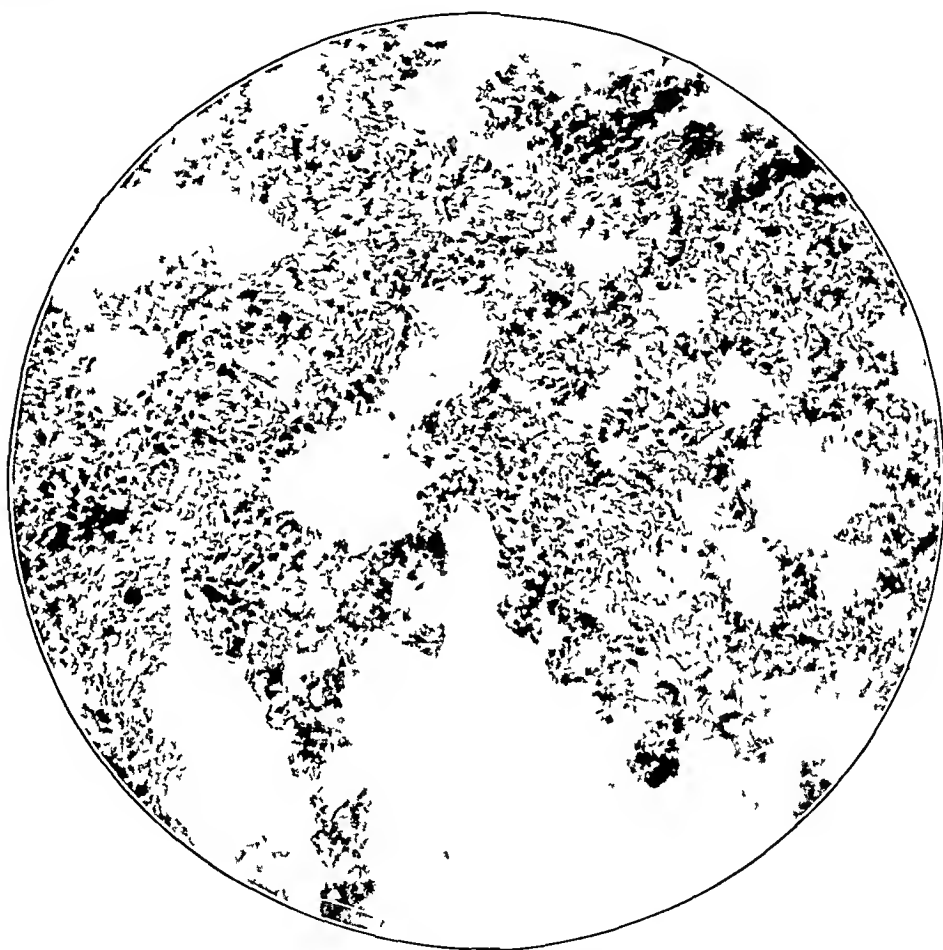


Fig 6—Showing considerable edema of the alveolar walls and hyperemia of the lungs

Carbon Dioxide Content—The decrease in carbon dioxide from about 50 to 30 cc was constant and strikingly similar to that of the acidosis of uremic coma in the human being

Kussmaul Picture—The usual progression of symptoms of muscle irritability, albuminuria, acidosis, vomiting, diarrhea, convulsions, Cheyne-Stokes breathing and coma and death, appeared constantly regardless of whether the ureter had been ligated or remained intact

With this in mind and the fact that on histologic survey so few changes were found in the kidneys, I am inclined to believe that involvement of the kidney is not pertinent to the production in a dog of disturbance which markedly parallels uremic coma in the human being

Blood Pressure—The blood pressure invariably went up in the animals used in these experiments, rising as high as 200 or 220 mm (McGregor method)

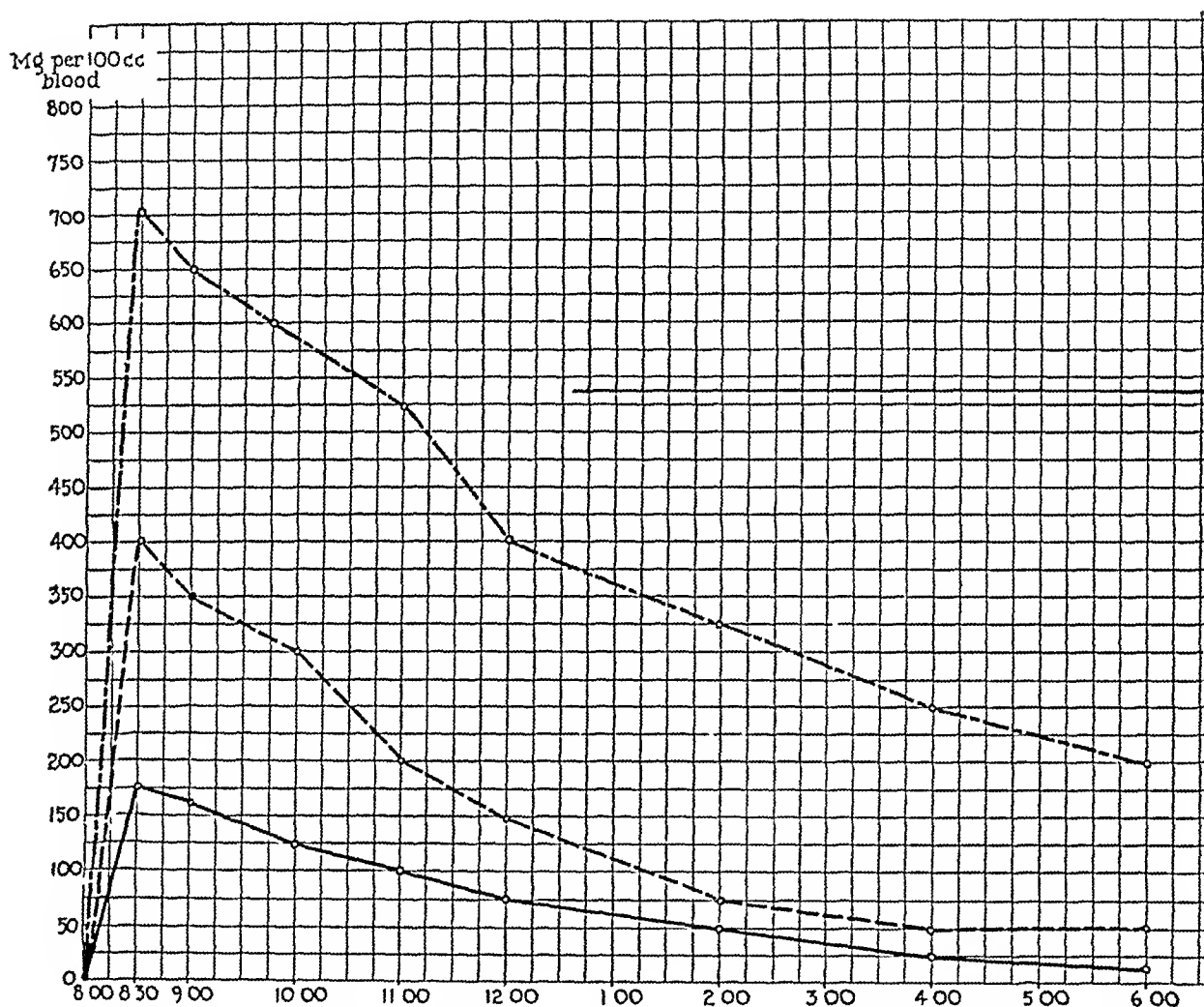


Fig 7—Experimental uremia Showing the reaction of urea in the blood after the intravenous injection of a 20 per cent solution of urea three times daily

CONCLUSIONS

- 1 Clinical uremia may be reproduced in all its features by the intravenous injection of from 10 to 20 per cent of a solution of urea
- 2 Intravenous injections of from 10 to 20 per cent of a solution of urea produces a marked enteritis
- 3 All features of uremia may be reproduced in presence of both kidneys

A REVIEW OF THE TECHNICAL METHODS OF DEMONSTRATING THE CIRCULATION OF THE HEART

A MODIFICATION OF THE CELLULOID AND CORROSION TECHNIC

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Many different methods have been employed in the anatomic study of the blood vessels, and all of these have been applied at one time or another in the study of the coronary circulation. The most important of these procedures may be grouped under the following headings

- 1 Dissection
- 2 Intravascular injection of dyes and other substances without clearing, roentgenography or corrosion
- 3 Serial sections
- 4 Impregnation methods
- 5 Injection of an opaque substance followed by roentgenography
- 6 Injection of a suitable mass followed by clearing
- 7 Injection of a comparatively stable mass followed by maceration or corrosion

REVIEW OF TECHNICAL METHODS

Dissection, in the hands of Galen, Vieussens and Haller, gave the first knowledge of the blood supply of the heart. This method, although its limitations are at once apparent, has been and always will be utilized by every earnest student of the coronary circulation. A systematic consideration of this field cannot be complete without careful control by dissection.

The injection of dyes and other substances for the purpose of recognizing the blood vessels, in gross as well as in microscopic sections,

1 Vieussens, quoted by Dragneff (footnote 12, first reference)

2 Lee, A. B. *The Microtome's Vade-Mecum*, ed 7, Philadelphia, P. Blakiston's Son & Company, 1913, p 258

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has been extensively used for many years. As this is one of the older methods, various substances have been utilized, from time to time, to suit the particular purpose of the various investigators, some of whom employed dyes such as saffron,¹ carmine,² Prussian blue,³ and India ink⁴ and silver nitrate,⁵ in aqueous solutions, in gelatin⁶ or mixed with various other ingredients.⁷ Others have experimented with injection masses including wax,⁸ starch mixtures,⁹ plaster of Paris,¹⁰ glue,¹¹ glazier's putty¹² (Teichmann's linseed oil masses¹³), asphalt¹⁴ (dissolved in benzene, ether or chloroform), India rubber¹⁵ (in carbon bisulphide); gum arabic¹⁶ (Bjeloussow's mass), sodium silicate,¹⁷ oil of sesame,¹⁸ shellac¹⁹

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9 Gage, S H Starch Injection-Mass, *J Roy Micr Soc* **8** 1056, 1888 Meyer, Hermann Modifizierte Form der Kleisterinjection, *Arch f Anat u Entwicklungsgesch*, 1882, p 60, Fernere Mittheilung über die Kleisterinjection, *ibid*, 1883, p 277 Pansch, A Noch einmal die Kleisterinjection, *ibid* **6** 76, 1881, Kalte Injection mit Kleistermasse, *ibid*, 1877, p 480 Wikszemski, Adam Eine Modification der von Pansch empfohlenen kalten Injection mit Kleistermasse, *ibid*, 1880, p 232

10 Bianchi, S, quoted by Spalteholz Cohnheim and von Schulthess-Rechberg Ueber die Folgen der Kranzarterienverschliessung für das Herz, *Virchow's Arch f path Anat* **85** 503, 1881 Erdos, Johann Eine Methode zur Injection der Blutgefasse mit kaltschüssiger Masse, *Anat Anz* **3** 261, 1888

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15 Frank, F, quoted by Mayer (footnote 4)

16 Erdos (footnote 10, third reference)

17 Jachtchinsky, S Sur l'emploi du silicate de soude (verre liquide) comme substance à injecter pour les préparations macroscopiques du système vasculaire, *Anat Anz* **24** 204, 1903 Roger, quoted by Unna (footnote 7, second reference)

(dissolved in alcohol), thymol²⁰ (Wywodzen's mass) and mercury²¹ No matter which substance was used, without further modifications the method could never be of much value except in microscopic work

Serial sections are valuable for more minute work Reconstructions have been made from sections,²² but obviously they can only serve for the study of limited areas

Methods of silver impregnation used by Hoyer and Unna depend on the fact that silver nitrate, when injected into the blood vessels or applied to sections of tissue, will deposit silver granules in the endothelial cells This technic has proved of great value in the study of the

18 Taguchi, quoted by Unna (footnote 7, second reference)

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21 Nuck, quoted by Bruhl (footnote 48)

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smaller vessels and the capillaries, particularly in microscopic sections. However, its field of usefulness must be limited to specialized researches.

The injection of an opaque material followed by roentgenography, because of the ease and rapidity with which it can be employed, has been used extensively in the study of the circulation in general, and especially in that of the blood supply to the heart. In 1896, shortly after the introduction of the roentgen ray, Teichmann's mass²³ and calcium sulphate²⁴ were each used to inject the blood vessels, and satisfactory roentgenograms were obtained. Since that time, many other opaque injection masses have been utilized. These include mercury alone,²⁵ mixed with other substances,²⁶ mercury salts,²⁷ the salts of barium,²⁸ bismuth²⁹ and calcium,³⁰ colloidal silver,³¹ red lead,³² lead

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chromate,³³ chrome yellow,³⁴ vermilion,³⁵ sodium bromide³⁶ and iodized oils³⁷ Pictures obtained in this manner, particularly stereoscopic, have been valuable in the visualization of circulatory networks, and this method is the only one now known by which one can hope to study the blood vessels of man during life Woollard³⁸ stated

By injection the x-ray pictures confirm the results already discovered by Spalteholz, for example, of the existence of anastomosis of the vessels of the heart On the whole, not much additional information has been obtained in this way Other methods, such as Spalteholz's clearing method, have been more useful

In 1907, Spalteholz³⁹ introduced a new method of studying the coronary circulation He injected both coronary arteries with chrome yellow gelatin, fixed the heart in 10 per cent solution of formaldehyde, bleached it with hydrogen peroxide, washed it in water, dehydrated it in alcohol and placed it first in benzene, then in a mixture of oil of wintergreen and benzyl benzoate and finally in a special tank to remove all of the air and benzene By this technic, the walls of the heart were cleared and rendered semitransparent, and as the injected vessels remained opaque, they could be readily traced through the cleared muscular structures This method is the one by which most of the recent advances in the knowledge of the coronary circulation, such as the existence of anastomosis, the blood supply to the mitral valve and the blood supply to the conduction system have been worked out The obvious reason why this method has proved superior to the roentgenographic method is that the former preserves the relationship of the blood vessels to the parts which they supply, while this relationship is lost in the stereoscopic roentgenogram, even though it may show a fairly complete picture of the entire vascular tree Spalteholz's

33 Parker (footnote 26, sixth reference)

34 Spalteholz, W, and Hirsch, C *Coronararterien und Herzmuskel, Anatomische und experimentelle Untersuchungen, Deutsche med Wchnschr* **1** 790, 1907 Spalteholz, W *Die Arterien der Herzwand, Leipzig, 1924, p 165*

35 Ferguson, F R *Roentgenological Injection Masses—Old and New, J Anat* **59** 297, 1924-1925 Hauch (footnote 32, third reference) Raw, N, quoted by Ferguson

36 Hinman, Morison and Lee-Brown (footnote 3, second reference)

37 Cadenat, F M, and Py *Endarterite obliterante du tronc axillo-humeral droit, Reperage du siege de l'obliteration par injection intra-arterielle de lipiodol, Extraction du caillot sans resultat, Bull et mem Nat Soc de chir de Paris* **50** 1149, 1924 Coffey, W B *Angina Pectoris, ed 1, New Orleans, A J Dickinson, 1927, p 104* Csapody, von J *Arterienphotographien vermittelt Lipiodol, Klin Wchnschr* **4** 2327, 1925 Rouslacroix *Exploration des arteres coronaires du coeur par l'injection lipiodelee, Compt rend Soc de biol* **93** 1446, 1925

38 Woollard, H *Recent Advances in Anatomy, Philadelphia, P Blakiston's Son & Company, 1927, vol 7, p 290*

39 Spalteholz (footnote 34, first reference)

method,⁴⁰ however, in spite of modifications which have been made by Bayne-Jones,⁴¹ Tandler,⁴² Gross⁴³ and Koch⁴⁴ has some definite limitations. The clearing is a slow process, and it is generally far from complete even in the smaller hearts, while in the larger ones the left ventricle is seldom rendered entirely transparent so that the picture of the coronary circulation presented is usually incomplete.

In many respects, the most important method is that of injections followed by corrosion or maceration. The corrosion is accomplished by allowing the injected preparations to remain in alkaline or strong acid solutions, the maceration is accomplished by decomposition with larvae and putrefactive bacteria.

Swammerdam⁴⁵ (1672), according to Unna, injected hot wax into the coarser blood vessels. He was also cited by Bruhl who said that he was the first to inject a mass which would become hard.

Bidloo⁴⁶ (1685) used Rose's metal (*vide infra*) for purposes of injection. After the injection, he boiled the parts to decompose the tissues surrounding the vessels.

Ruysch⁴⁷ (1704) forced a metal of secret composition into the coronary vessels and then allowed larvae and maggots to attack and disintegrate the muscle tissue. His description of the coronary arteries has not met with the approval of later writers. Unna, for example, agreed with Hyrtl that the injections made by Ruysch were, in the main, extravasations and consequently inaccurate.

Bruhl⁴⁸ said that Lieberkuhn⁴⁹ (1711-1746) was the first to use true corrosion. He used Swammerdam's mass (wax, mixed with fats, and stained with cinnabar) and corroded the parenchyma with nitric acid. Swammerdam's mass, according to Unna,⁵⁰ was also used by Alexander Monro (1730), Schacher (1710), Fabricius (1741), Cassebohm (1740), Barth (1773) and Prochaska (1810).

40 Spalteholz (footnote 34, second reference)

41 Bayne-Jones, S. The Blood Vessels of the Heart Valves, *Am J Anat* **21** 449, 1917

42 Tandler, J. Anatomie des Herzens, in Karl von Bardeleben's *Handbuch der Anatomie des Menschen*, Jena, Gustav Fischer, 1913, vol 3, pt 1, p 292

43 Gross (footnote 22), (footnote 28, second reference)

44 Koch, Walter. Ueber die Blutversorgung des Sinusknotens und Etwaige Beziehungen des letzteren zum Atrioventrikularknoten, *Munchen med Wchnschr* **56** 2362, 1909

45 Swammerdam (footnote 8, second reference)

46 Bidloo, quoted by Bruhl (footnote 48)

47 Ruysch, F, quoted by Spalteholz and others

48 Bruhl, Gustav. Die anatomischen Darstellungsweisen der Hohlräume des Ohres und der Nase, *Anat Anz* **14** 418, 1898

49 Lieberkuhn, quoted by Bruhl (footnote 48)

50 Unna (footnote 7, second reference)

It is to Hyrtl⁵¹ (1855), however, that credit for most of the development of corrosion technic is due. Bruhl called him the master of corrosion. He used various metals of a low melting point but did most of his work with wax, mixing one part of it with six parts of resin. The actual corrosion was done with hydrochloric acid.

Hoyer⁵² (1877) found that solutions of shellac thinned with alcohol made the best injection masses for gross and fine vessels. He claimed that this mass could be used in making corrosion preparations and advised the addition of cinnabar as a coloring material when it is used for this purpose.

Altmann⁵³ (1879) injected blood vessels with olive oil, treated the part with osmic acid, froze it and then placed it in Javelle water⁵⁴ for corrosion. Only small sections could be used by this method. The osmic acid hardened the olive oil in the vessels and, since fats are more resistant to acids, they were not as quickly corroded as the tissues. The time necessary for corrosion varied from a few minutes to several hours, and if the action was continued too long the injection mass crumbled. Consequently, this method has not been widely adopted.

Muller⁵⁵ (1906) utilized a metal of low melting point, and Flint⁵⁶ used Wood's metal and celloidin for studying the structure of the lungs. Ten per cent potassium hydroxide was used for corrosion.

Lipowitz's metallic alloy of low melting point (from 65 to 70 C), containing cadmium, tin, bismuth and lead, was employed by Nussbaum⁵⁷ (1912) for injections in the coronary circulation. Since hydrochloric acid attacked this alloy, he found it necessary to use 15 per cent potassium hydroxide to remove the soft parts. His preparations for corrosion of the coronary circulation are the best that have ever been obtained with metals.

Ghoreyeb⁵⁸ (1916) injected the coronary arteries with Wood's metal in order to determine their capacity. Corrosion was carried out in order to recover the metal.

51 Hyrtl, quoted by Bruhl (footnote 48), quoted by Spalteholz.

52 Hoyer (footnote 19, first reference).

53 Altmann, R. Ueber die Verwerthbarkeit der Corrosion in der mikroskopischen Anatomie, *Arch f mikr Anat* **16** 471, 1879.

54 A solution of sodium hypochlorite prepared by adding soda ash to a solution of calcium hypochlorite.

55 Muller, Josef. Zur vergleichenden Histologie der Lungen unserer Haus-saugetiere, *Arch f mikr Anat* **69** 1, 1906.

56 Flint, J. M. The Development of the Lungs, *Am J Anat* **6** 1, 1906-1907.

57 Nussbaum, Adolf. Ueber das Gefasssystem des Herzens, *Arch f mikr Anat* **80** 450, 1912.

58 Ghoreyeb, A. A. Studies on the Circulation. I. The Effect of Disease on the Renal Arterial Bed, II. The Capacity of the Coronary Arteries as Related to Weight and Age of the Heart, *J. M. Research* **35** 87, 1916-1917.

The injection of a celloidin or celluloid mass into the blood vessels, followed by corrosion of the tissues, has been used for many years and by various investigators. It was first employed by Schiefferdecker⁵⁹ (1882), who prepared a mass of celloidin, dissolved in concentrated alcohol and ether, and colored by asphaltum, Berlin blue or cinnabar. Digestion was performed by hydrochloric acid. Hochstetter⁶⁰ (1886) claimed that he began using celloidin at the same time, but independently of Schiefferdecker. He recommended the addition of kaolin because of the shrinkage of the casts obtained by Schiefferdecker's method. His masses were colored with cobalt blue, chrome yellow or cinnabar. Storch⁶¹ (1898) made three distinct improvements in the celloidin technic: (1) the employment of acetone as a celloidin solvent, (2) the injection of a thicker mass (after a preliminary injection of a thin one) to insure a firm cast of the larger trunks, and (3) the prevention of shrinkage by the substitution of celluloid for celloidin. Peabody⁶² (1897) used Prussian blue as a coloring agent in the injection of the lateral line canals in the smooth dogfish. Brodel⁶³ (1901) claimed to have used Schiefferdecker's corrosion method as modified by Mixer and Mall,⁶⁴ employing an alcohol and ether solution of celloidin. Digestion was performed by pepsin dissolved in hydrochloric acid.

Flint⁶⁵ (1901) used both commercial celluloid and a mixture of celloidin⁶⁶ and camphor dissolved in acetone. The addition of camphor was a definite improvement, for it prevented the shrinkage of the casts and made it unnecessary to preserve them in glycerin. Flint recommended corrosion of the tissues in concentrated hydrochloric acid.

59 Schiefferdecker, P. Ueber die Verwendung des Celloidins in der anatomischen Technik, *Arch f Anat u Entwicklungsgesch*, 1882, p 199.

60 Hochstetter, Ferdinand. Ueber eine Modifikation der Schiefferdeckerschen Celloidinkorrosionsmasse, *Anat Anz* **1** 51, 1886.

61 Storch, Carl. Das Celluloid und seine Anwendung zur Injektion von Blutgefassen, *Ztschr f Tiermed* **3** 173, 1898.

62 Peabody. The Ampullae of Lorenzini of the Selachii, *Zool Bull, Boston* **1** 163, 1897-1898.

63 Brodel, Max. The Intrinsic Blood Vessels of the Kidney and Their Significance in Nephrotomy, *Bull Johns Hopkins Hosp* **12** 10, 1901.

64 Mall, F. P. A Study of the Structural Unit of the Liver, *Am J Anat* **5** 228, 1906.

65 Flint, J. M. The Ducts of the Human Submaxillary Gland, *Am J Anat* **1** 269, 1901-1902.

66 Celloidin is a concentrated preparation of pyroxylin. Celluloid is essentially pyroxylin and camphor. Satisfactory preparations are not made with celloidin unless camphor is added. Since the addition of camphor to celloidin forms celluloid, it would seem more proper to speak of those preparations containing both celloidin and camphor as celluloid injection masses, even though this does not conform to general usage.

rather than by the slower method of digestion by pepsin Krassuskaja ⁶⁷ (1904) also used a mass of photoxylm (or celloidin) and camphor in acetone

In 1906, Huber, ⁶⁸ after having experimented with various dyes, introduced alkanin, a red pigment, which is soluble in acetone and can be used for the smallest vessels without causing crumbling of the preparations He introduced a constant pressure device by attaching the cannulas by rubber tubing to a tank of compressed air He found that a sudden release of a high pressure (from 20 to 25 pounds [from 9 to 11 Kg]) at the onset was necessary in the injection of the finer vessels, and suggested a stock solution of the injection mass containing 30 Gm of celloidin and 20 Gm of camphor dissolved in 600 cc of acetone Marshall ⁶⁹ (1923) mixed 10 per cent solutions of crystal violet and brilliant green to make a permanent blue for celluloid preparations Morison ⁷⁰ (1923) found that old roentgen-ray films could be used as a cheaper means of obtaining celluloid, but considered them satisfactory only in the preparation of coarser specimens He recommended the substitution of a more concentrated solution of the mass after the injection had been running for ten or fifteen minutes in order to obtain a solid cast of the larger vessels The casts were kept in a preservative solution containing 100 cc of water, 2 cc of solution of formaldehyde and 20 cc of glycerin Terry and Delamere ⁷¹ (1924) used this technic in studying the circulation of adenomas of the thyroid gland

Counseller and McIndoe ⁷² (1926) forced cold water through the vessels of the liver to remove the blood and bile Weights were then placed on the specimens, and they were wrapped in towels to remove as much of the fluid as possible Their other modifications were the utilization of artist's oil paints for coloring, the lengthening to two days of the time that the injection was continued under constant pressure and the adoption of a dry method of mounting the corrosion preparations, using the technic described by Lundquist and Robertson ⁷³ Barker ⁷⁴ (1927) followed the technic described by Counsellor and

67 Krassuskaja, A Abstr by Stieda, Anat Hefte **13** 521, 1904

68 Huber, G C The Arteriolae Rectae of the Mammalian Kidney, Am J Anat **6** 392, 1906-1907

69 Marshall, J A Method for Preparing Blue Celluloid Injection Material, J A M A **80** 181 (Jan 30) 1923

70 Morison (footnote 3, second reference)

71 Terry and Delamere (footnote 4, third reference)

72 Counseller, V S, and McIndoe, A H Dilatation of the Bile Ducts (Hydrohepatosis), Surg Gynec Obst **43** 729, 1926

73 Lundquist, L R, and Robertson, H E The Dry Mounting Method for Museum Specimens, Hosp Prog **7** 273, 1926

74 Barker, N Personal communication to the author

McIndoe, except that he increased the time of injection from two to five days or even longer. Scott and Moore⁷⁵ (1928) believed that any homogeneous mass with a relative viscosity of 18.5 (as compared to water) is sufficient for injection of the renal circulation to, but not beyond, the efferent glomerular arteries. For celloidin, they found that a solution of this viscosity contained 2.75 per cent celloidin and 2 per cent camphor dissolved in acetone.

Although celluloid and celloidin have been used as injection masses for a considerable length of time, I have not been able to find more than three references to their use in the study of the coronary vessels. Kerr and Mettier⁷⁶ (1925) published two photographs of injections of celloidin in the coronary arteries in man made by Faulkner and Epstein, but they failed to show relationships because a cast was not made of the interior of the heart. Spalteholz⁷⁷ discouraged the use of celloidin, and his influence has probably done much to keep this material from being used more extensively as an injection mass of the coronary vessels. Quite recently (1928) Wearn⁷⁸ employed thick masses of celloidin as well as wax in studying the thebesian vessels. Corrosion was not attempted.

In demonstrating the coronary circulation, a cast of the interior of the heart should be made, otherwise, the parts supplied by each vessel remain obscure. It is surprising that so little work of this nature has been undertaken. Bruhl, in discussing corrosion preparations of the cavities in and around the ear and nose, mentioned the following materials that have been employed: (1) wax resin, (2) paraffin, (3) metals of low melting point, including Aicet's metal (one part lead, two parts tin, two parts bismuth), Rose's metal (one part lead, one part tin, two parts bismuth) and Wood's metal (eight parts lead, four parts tin, sixteen parts bismuth, three parts cadmium) and (4) celloidin.

The first two substances have been utilized in the measurement of the capacity of the chambers of the heart. Periot⁷⁹ and Gaston⁸⁰ (1925) made plaster-of-paris casts of the left ventricle. They cited

75 Scott, Ernest, and Moore, R. A. Vascular Injection in Pathology, *J. Lab. & Clin. Med.* **13** 481, 1928.

76 Kerr, W. J., and Mettier. The Circulation of the Heart Valves, Notes on the Embolic Basis for Endocarditis, *Am. Heart J.* **1** 96, 1925-1926.

77 Spalteholz, W. Die Arterien der Herzwand, text and footnote, 1924, p. 5.

78 Wearn, J. T. The Role of the Thebesian Vessels in the Circulation of the Heart, *J. Exper. Med.* **47** 293, 1928.

79 Periot, M. Casts of the Interior of Heart Cavities, *Compt. rend. Soc. de biol.* **92** 615, 1925.

80 Gaston. Un procede d'etude de la morphologie des cavités cardiaques, *Compt. rend. Soc. de biol.* **92** 614, 1925.

Collin, Hiffelsheim and Robin⁸¹ (1864) and Tandler⁴² as having made casts of the cardiac cavities previous to their work and stated that, except for them, investigators had not used casts in determining the size of these cavities. Tandler published photographs of casts of the interior of the heart in his work on anatomy. According to Gaston, all these observers poured melted wax or paraffin into the heart.

Nussbaum⁵⁷ (1912) seems to have been the only one to make casts of the cardiac cavities with metals. He filled the heart with paraffin. Eight days later, he melted out the paraffin and replaced it with Lipowitz metal, which was similar to the other metals of low melting point, containing three parts of cadmium, four parts of tin, eight parts of lead and fifteen parts of bismuth, this metal had the same melting point as Wood's metal (from 65 to 70 C) and was identical with that substance except that it contained one less portion of bismuth. Excellent casts of the heart and of the coronary vessels were obtained.

Although celluloid and celloidin have been used in the pelvis of the kidney (by Morison,⁷⁰ Barker⁷⁴ and others) and in the cavities in and about the nose and ear,⁸² I have not found any reference to their use in the molding of casts of the cardiac cavities. In fact, I have found no reference to their use in the making of casts of any structure as large as the interior of the adult heart. It seems advisable, therefore, to publish the modifications of the celluloid technic which have been found necessary for the injection of the cardiac cavities.

A MODIFICATION OF THE CELLULOID AND CORROSION TECHNIC

Apparatus—The apparatus which I have employed is almost identical with that used by Counseller and McIndoe in making injections in the bile ducts of the liver (fig 1). Constant air pressure is used instead of the gas which is shown in the diagram. The mercury manometer aids in adjusting the pressure accurately. A second mercury manometer is also needed, as a lower pressure is used in injections in the interior of the heart. Three of the small bottles for the injection mass are needed for each heart in which injection is to be made. By means of Y-tubes and additional connections of rubber tubing, injections can be performed in any number of hearts at one time. The hearts are kept in a bath of running, cold water while the injection is in progress. This delays disintegration and aids in dissolving the acetone from the injection mass.

⁸¹ Collin, Hiffelsheim and Robin, quoted by Periot (footnote 79) and Gaston (footnote 80).

⁸² Siebenmann, quoted by Bruhl (footnote 48). Steinbruge, H. Zur Corrosions-Anatomie des Ohres, *Centralbl f d med Wissensch* **23** 545, 1885.

Stock Solution—The injection mass is prepared in a concentrated form. The constituents of the stock solution, which is the same as Morison's solution C, are as follows: 100 Gm old roentgen-ray films, 80 Gm pure gum camphor, and 1,000 cc of acetone. The emulsion is scrubbed off the films in warm water, and the films are cut into small pieces so they will dissolve more readily in the acetone. The stock bottle should be inverted every day so the films may become dissolved more rapidly. The mechanical stirring and the filtration described by

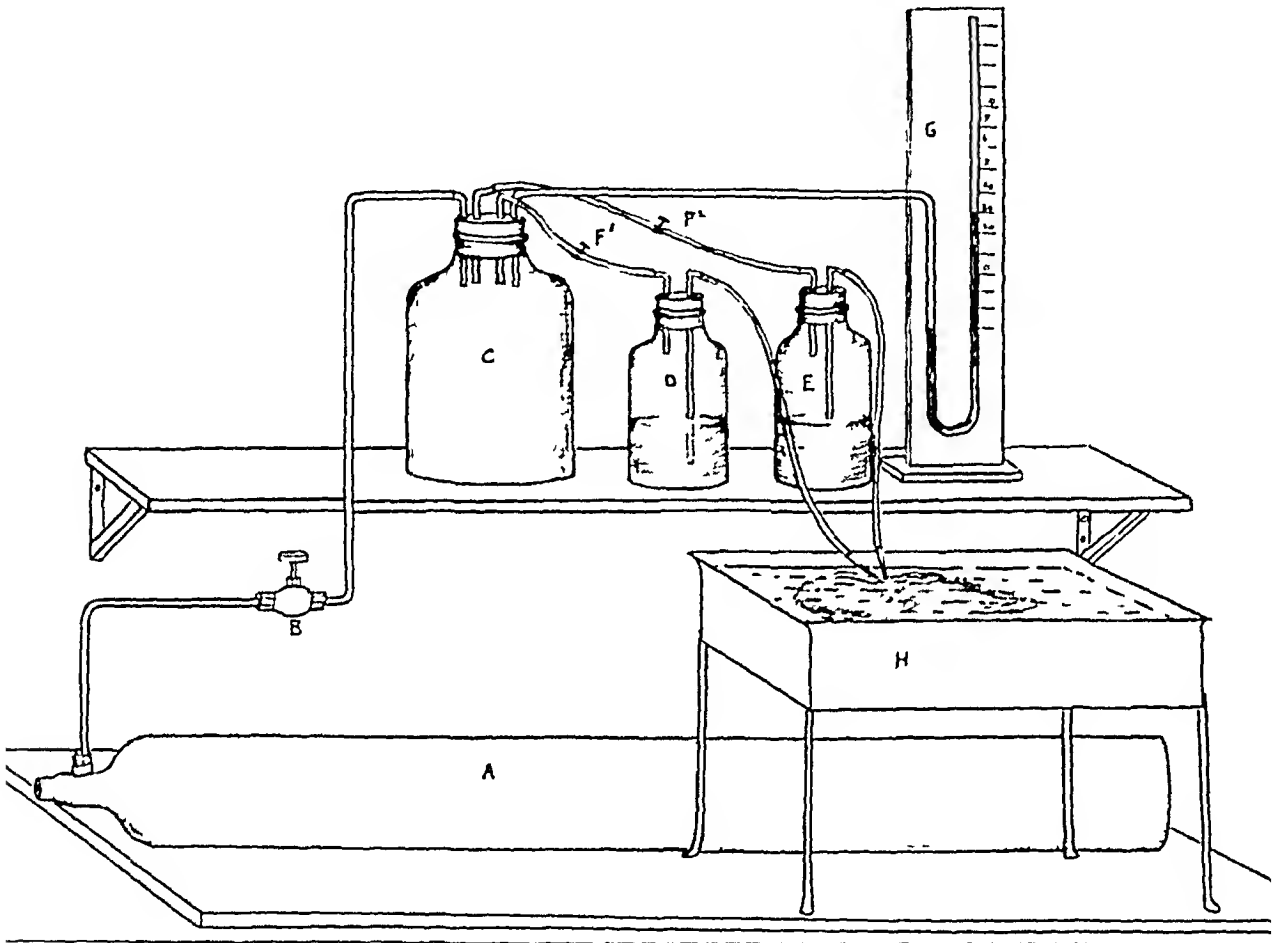


Fig 1—Injection apparatus (from Counsellor and McIndoe) A, gas tank, B, needle valve, C, lead bottle, D, injection bottle, E, injection bottle, F', F'', stopcocks, G, mercury manometer, H, specimen tank

Morison have not been found necessary. In five or six days the mass is ready to use. The dilution of the stock solution for purposes of injection is discussed elsewhere. Artist's oil paints, as recommended by Counsellor and McIndoe, have proved satisfactory coloring materials. The paints must be well mixed in the solution immediately before the injection is started. As a routine I have used Prussian blue for the right coronary artery, vermillion for the left and silver white for the veins and the casts of the heart chambers.

Preparation of the Specimen—Injections are much more easily performed in the heart and vessels if care is taken in the removal of the specimen at necropsy. The heart and lungs, together with that portion of the diaphragm which surrounds the inferior vena cava, are removed en masse. Then the heart and great vessels are dissected free from the lungs and diaphragm, care being taken to have the stumps of the great vessels as long as possible. This necessitates cutting the pulmonary vessels close to the lungs.

The chambers of the heart should be washed thoroughly with water. The water must be forced through in the direction of the blood flow of the heart, that is, the stream must be directed into either the superior or the inferior vena cava to wash out the right side and into one of the pulmonary veins to remove the blood clots from the left side of the heart. A massage of the heart will aid in removing some of the clots. Others will have to be extracted with forceps. All must be removed if a perfect cast is to be obtained.

Technic of Arterial Injections—The injection of the arteries is not particularly difficult and is not unlike the injection of the portal vessels or the renal arteries, which has been well described by others⁸³. The aorta must be cut down longitudinally toward the heart until the coronary arteries are seen, but not so far that it would be impossible to tie off the vessel later. Then the cannulas must be inserted through the orifices of the coronary arteries and tied firmly in place. In order that this may be done, the first part of each coronary artery must have been freed previously, and ligatures passed beneath the vessels. The ligatures (two or three for each cannula) are then tied firmly and so tight that the cannula will not slip if twisted slightly. The cannulas must be inserted when the heart is quite fresh, otherwise they or the ligatures are likely to cut through the vessels.

The coronary arteries are each washed with water at a pressure of 250 mm. of mercury until the water is no longer blood-tinged. An effort is not made to remove the water from the vessels before the injection is started, since water hardens the mass. Although the arterial injections are not started until the veins and the chambers of the heart have become distended with the mass, they will be commented on first for the sake of simplicity.

A 1:4 or 1:5 dilution of the stock solution (one part of the stock solution to four or five parts of acetone) is generally used for the arterial injection. This dilution assures the injection of the smaller vessels. Artist's oil paint is added to color the solutions, vermilion being used for the left coronary artery and Prussian blue for the right

⁸³ Counsellor and McIndoe (footnote 72). Hildebrand (footnote 26, third reference).

The celluloid mass, after being well mixed, is injected into both coronary arteries simultaneously at an initial pressure of about 450 mm of mercury, and is maintained at this pressure for an hour or two, after which the pressure is reduced to one ranging from 150 to 250 mm at which the injection is continued for from five to seven days. To strengthen the larger trunks, a more concentrated solution (1 2 or 1 3 dilution of the stock solution) should be substituted within the first four hours. If the injection is not continued for from five to seven days, the larger vessels are likely to be hollow and consequently fragile.

Technic for Molding Casts of the Cavities and the Veins—After the cavities of the heart have been washed free of blood clots, the foramen ovale is opened, by enlarging the opening, if patent, or by passing the points of blunt scissors or forceps through the thinnest portion of the interauricular septum (through the fossa ovalis) and spreading the points of the instrument until the opening is adequate. If this is not done there will not be a point of union between the casts of the two sides of the heart, and the preparation will fall apart after corrosion. One wide-tipped glass cannula is placed in the orifice of either the superior or the inferior vena cava, and another is placed in the opening of one of the pulmonary veins. Both cannulas are tied securely. All the other great vessels are then tied successively. It is rather difficult to ligate the aorta owing to the two cannulas (one to each coronary artery) within it. This can be accomplished, however, so that there is not any leakage, if the aorta has been divided longitudinally, each half being wrapped around the adjacent cannula and tied securely in several places, and finally the two portions of the aorta being tied firmly together. If any of the great vessels have been cut too short, the opening can be closed by inserting a tightly fitting cork into the lumen, the large end inward, and tying the stump of the vessel over the cork. When every orifice is closed, rubber tubing is attached to the cannula in the vena cava and to the one in the pulmonary vein. The tubing to the latter may be clamped, as generally the left side of the heart will fill from the right. If, for any reason, the left side of the heart does not fill, and this occasionally happens, celluloid may readily be injected through the otherwise unused cannula into the pulmonary vein.

The celluloid mass is forced into the cavities of the heart with the same apparatus with which injections are made in the arteries. When it is desired to make an injection in the veins of the heart, a thin solution should be used first. For this purpose, a solution of one part of the stock solution to three or four parts of acetone, to which artist's oil paint (white) has been added for coloring, is used. This solution must be stirred until it is well mixed. After 500 cc has been emptied

into the heart, a thick solution is substituted. The stock solution may be used for this purpose, but the mass generally flows in a little more readily if it is thinned slightly with acetone. An effort must be made to tie off all leaks that may occur when the celluloid is injected. The smaller leaks will be closed by the injection of a thicker celluloid mass. I attempt to use continuous injection at a pressure of from 20 to 60 mm of mercury in filling the cavities, but if leakage occurs this may not be possible at the onset. When leakage takes place, pressures ranging from 60 to 120 mm of mercury are used, but only long enough to allow the celluloid to flow in until the auricles are rendered slightly tense to palpation. The pressure is then clamped off and the process repeated about every half hour during the first day and about every one to three hours thereafter. When there is no leakage, the injection is continued until soft areas cannot be palpated on the surface of the auricles and until the cannulas are firmly cemented in. A uniform cast rather than a solid cast is desirable, hence, it is necessary to turn the heart in various positions from time to time as the celluloid tends to become deposited in the dependent portions. It is sometimes necessary to puncture the walls of the auricles with a hypodermic needle and inject water before the mass in the cavities will harden. This allows the air and acetone to escape, makes room for more of the mass to enter and supplies fresh water to remove the acetone and to precipitate the celluloid.

The injection of the veins and of the cast is begun first so that the arteries will not be stretched after the arterial injection has been started. The injection of the arteries is continued uninterruptedly for from five to seven days, and that of the interior of the heart for from five to fourteen days, depending on the size of the heart and on other variable factors.

Corrosion—When the injection is considered completed, the heart is placed in concentrated hydrochloric acid and allowed to remain there for from five to fifteen days depending on the thickness of the myocardium and the rate of its corrosion.

Washing—When the corrosion is completed, the heart is immersed in water and a fine stream is directed against it to wash away everything but the cast. It is important to direct this stream so that it strikes just below the surface of the water. This allows the corroded tissues to float away and minimizes the injury to the smaller vessels. The washing does not have to be completed at once, in fact, washing is more easily carried out if the specimen is allowed to stand over night in water. If all the tissues cannot be washed away, the specimen should be placed again in fresh concentrated hydrochloric acid and left there for from twelve to twenty-four hours. Sometimes it is difficult to remove the epicardial fat. This can be remedied by placing the heart in xylene

for a few hours, which will dissolve out the fat without injury to the cast. The heart is then washed again with water to remove the adhering particles of fat and the xylene.

Preservation—After the washing is completed, the specimen is allowed to stand in water to which enough sodium bicarbonate has been added to neutralize the acid that may still be present. A coating

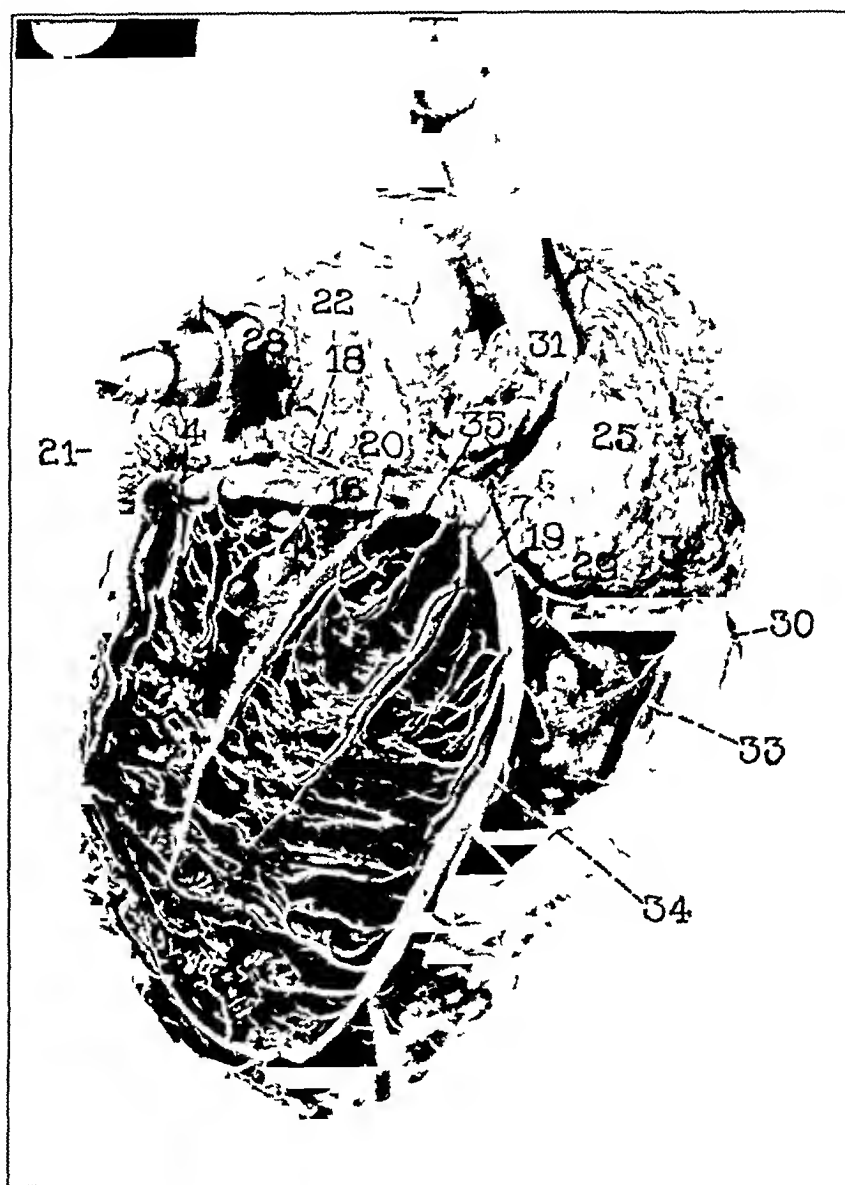


Fig 2—Posterior view of celluloid cast of heart from a girl, aged 10 years, who had died from generalized peritonitis, 21, left auricular appendage, 22, left auricle, 25, right auricle, 31, inferior vena cava, 28, left pulmonary veins, 4, left circumflex artery, 32, right coronary artery, 33, posterior artery of right ventricle, 34, posterior descending artery, 7, posterior artery of left ventricle, 35, accessory posterior artery of left ventricle, 19, vein of posterior inter-ventricular sulcus, 29, right coronary vein, 20, posterior vein of left ventricle, 16, coronary sinus, 18, oblique vein of Marshall, 30, vein of acute margin

of varnish is applied with a fine spray from an atomizer, it is better to delay this procedure until all photographs have been taken. The

preparations can be mounted dry according to the method of Lundquist and Robertson, or wet, using the solution of water, formaldehyde and glycerin described by Morison

The Finished Preparations—The completed specimen shows the left coronary artery injected in red, the right coronary artery in blue and the coronary veins in white. Figures 2 to 4 are actual photographs of specimens in which injections were made. The wall of the heart has

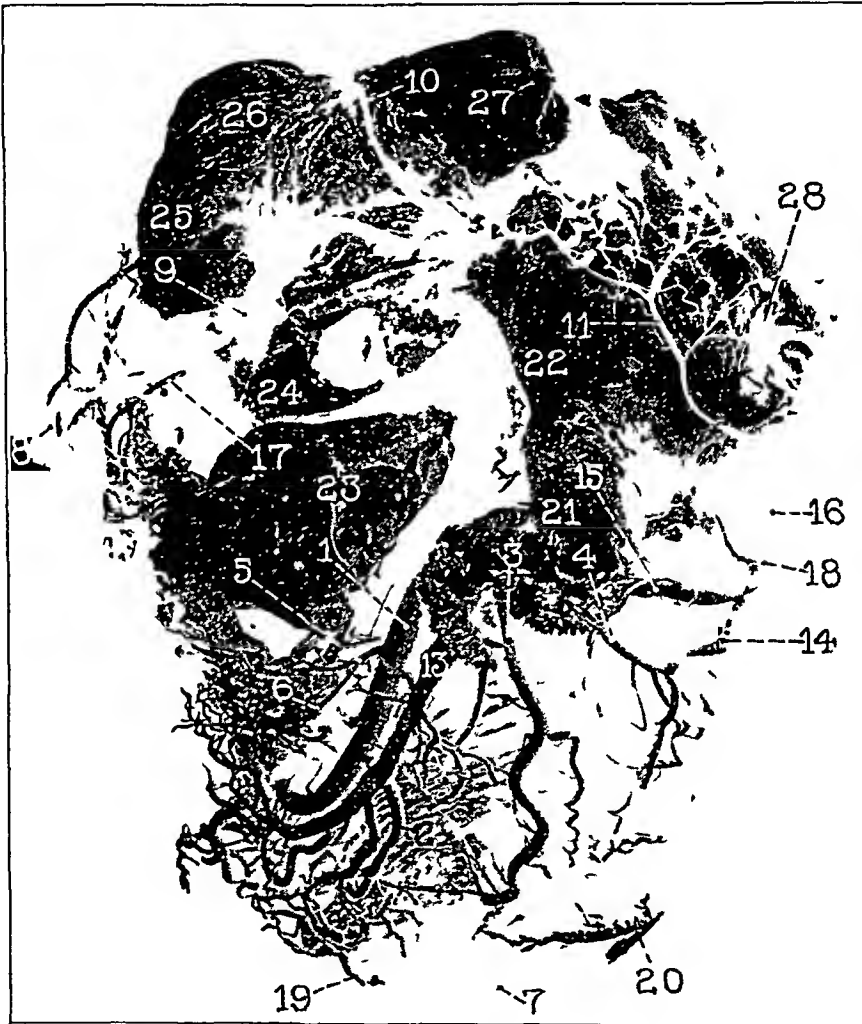


Fig 3—Anterosuperior view of celluloid cast of heart of woman, aged 44, who died from carcinoma of the rectum, 21, left auricular appendage, 22, left auricle, 23, pulmonary artery, 24, aorta, 25, right auricular appendage, 26, right auricle, 27, superior vena cava, 28, left pulmonary veins, 1, anterior descending artery, 2, first accessory anterior descending artery, 3, second accessory anterior descending artery, 4, circumflex artery, 5, artery to conus arteriosus, 6, artery to interventricular septum, 7, posterior artery of left ventricle, 8, anterior arteries of right ventricle, 9, anterior artery of right auricle, 10, artery of crista terminalis (artery to sinus node), 11, intermediate artery of left auricle, 13, vein of anterior interventricular sulcus, 14, vein of obtuse margin, 15, left coronary vein, 16, coronary sinus, 17, anterior vein of right ventricle, 18, oblique vein of Marshall, 19, vein of posterior interventricular sulcus, 20, posterior vein of left ventricle

been corroded, and the background is the white cast of the chambers of the heart which accurately depicts the internal surface of the heart and thus preserves the normal relations of the coronary vessels, although none of the structures of the living heart remains. All four cavities of the heart have been expanded at the same time, under the same pressure, which is relatively low.

Advantages—This method of studying the coronary arteries seems to have several distinct advantages over the usual methods, such as



Fig 4—Anterior view of celluloid cast of heart of child, aged $13\frac{1}{2}$ months, who died during anesthesia, 25, right auricle, 36, right ventricle, 21, left auricular appendage, 38, valve of Vieussens, 1, anterior descending artery, 2, first accessory anterior descending artery, 37, second accessory anterior descending artery, 4, circumflex, 16, coronary sinus

injection of opaque materials followed by the taking of roentgenograms, clearing with oil of wintergreen or glycerin, or corrosion without molding a cast of the heart. A cold injection mass is used. The celluloid cast of the interior of the heart shows the size, shape and contour of the chambers, forms a support for the blood vessels and

depicts relationships even after all the tissues of the living heart have been corroded away. The completed injections enable a casual observer to form a fairly accurate impression of the course and relations of the coronary vessels and on that account should be of considerable value in the teaching of anatomy. All structures are in three dimensions, hence, there need not be any confusion in their interpretation, as often occurs with roentgenograms or even stereoroentgenograms. Injections are made in all the veins, whether or not they empty into the coronary sinus. The casts adapt themselves readily to photography. Lastly, celluloid injected into the arteries penetrates to the capillaries but not through them, and, for this reason, the resulting cast is an accurate picture of the arterial tree uncomplicated by venous branches.

Disadvantages—The chief disadvantage of this method of injection is that it is practically impossible to take microscopic sections of the heart either before or after the injections are made. In addition, while celluloid is flexible, it is nevertheless fragile and must be handled with care, for a broken vessel cannot be replaced.

ATOPY

BLOOD CALCIUM AND GASTRIC ANALYSIS ¹

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AND

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A study of the blood calcium in 167 cases of asthma and allied conditions is presented in the hope of helping to define the importance of calcium determination and calcium treatment in atopic or allergic conditions. The second part of this paper is a preliminary report on the analysis of the gastric contents in fifty cases of atopy.

CALCIUM METABOLISM IN ATOPY

A discussion of this phase of the subject is closely related to the various theories explaining the pathogenesis of asthma and of allied conditions. It is a fairly well established fact that these conditions are due to a form of hypersensitiveness either to some extrinsic protein or to an infection usually of the upper respiratory tract. There are those who insist on the reflex origin of asthma, and somewhat associated with the latter theory is the explanation advanced by Pottenger,¹ who feels that in asthma there is a relative deficiency of calcium ions in the cells of the bronchial system with an imbalance in favor of the potassium ions. This deficiency of calcium results in a lessened irritability of the sympathetic nerve, while the excess of potassium stimulates the parasympathetic or vagus nerve, so that vagotonia and hence bronchospasm and asthma result, therefore, administration of calcium restores the equilibrium, eliminates vagotonia and improves the condition of the patient.

In close relation to these views, a considerable literature is found in which an attempt is made to prove the presence of such a deficiency and the specific value of calcium therapy. These observations, however, have not gone unchallenged, and it is for this reason that the present study was undertaken. It is necessary to agree as to what constitutes a normal

¹ From the Department of Medicine and Biochemistry, University of Pittsburgh School of Medicine.

Read before the Society for the Study of Asthma and Allied Conditions, Washington, D C, April 28, 1928.

¹ Pottenger, F M. A Discussion of the Etiology of Asthma in its Relationship to the Various Systems Composing the Pulmonary Neurocellular Mechanism with the Physiologic Basis for the Employment of Calcium in its Treatment, *Am J M Sc* **167** 203, 1924.

blood calcium A survey of the literature reveals that from 9 to 11 mg per hundred cubic centimeters of blood is considered normal Thus, according to Groves and Vines² the average figure is 10.5 mg According to Halverson,³ it is 10.2 mg, with a variation of from 9.6 to 10.8 mg According to Schwartz and Levin,⁴ it is from 9 to 12 mg, while Myers⁵ finds it to be between 9 and 11 mg, and Caven and Cantarow⁶ place it between 6.5 and 9.5 mg per hundred cubic centimeters of blood Forty specimens of blood were obtained from normal subjects, medical students, and the blood calcium determined by the use of the Tisdal technic Twenty-seven of these were obtained on a fasting stomach and thirteen, two hours after breakfast The lowest reading in the whole series was 8.5 mg, and the highest was 11.7 mg, with an average of 10.43 mg of calcium per hundred cubic centimeters of blood It is interesting to note that there was not any appreciable difference in the average value obtained in the fasting blood from the nonfasting blood, the figure for

TABLE 1—*Blood Calcium in Various Atopic Conditions and in a Normal Person*

	7.5 to 8 Mg	8 to 8.5 Mg	8.5 to 9 Mg	9 to 9.5 Mg	9.5 to 10 Mg	10 to 10.5 Mg	10.5 to 11 Mg	11 to 11.5 Mg	11.5 to 12 Mg	12 to 13 Mg	Num ber of Cases	Average Calcium
Asthma	0	4	6	6	16	22	15	6	2	3	80	10.08
Hay fever	0	0	0	3	5	14	8	6	2	4	43	10.55
Atopic rhinitis	0	1	0	2	2	8	2	3	1	2	21	9.95
Urticaria	2	3	0	3	4	5	3	1	0	0	21	9.66
Angioneurotic edema	0	0	0	0	0	2	0	0	0	0	2	10.4
Normal	0	2	0	2	6	17	11	1	1	0	40	10.43
Total series	2	10	6	16	33	68	39	17	6	9	207	10.19

the former being 10.1 mg, while the latter was 10.34 mg Table 1 shows that most of the readings were closely grouped

An analysis was then made of the observations on the blood calcium in 167 cases of atopy, comprising (table 1) eighty cases of asthma, forty-three cases of hay-fever, twenty-one cases of atopic or vasomotor rhinitis, twenty-one cases of urticaria and two cases of angioneurotic

2 Groves, W. R., and Vines, H. W. C. The Control of Hemorrhage by Intramuscular Injection of Calcium Chloride, *Brit. M. J.* **2**: 40, 1921

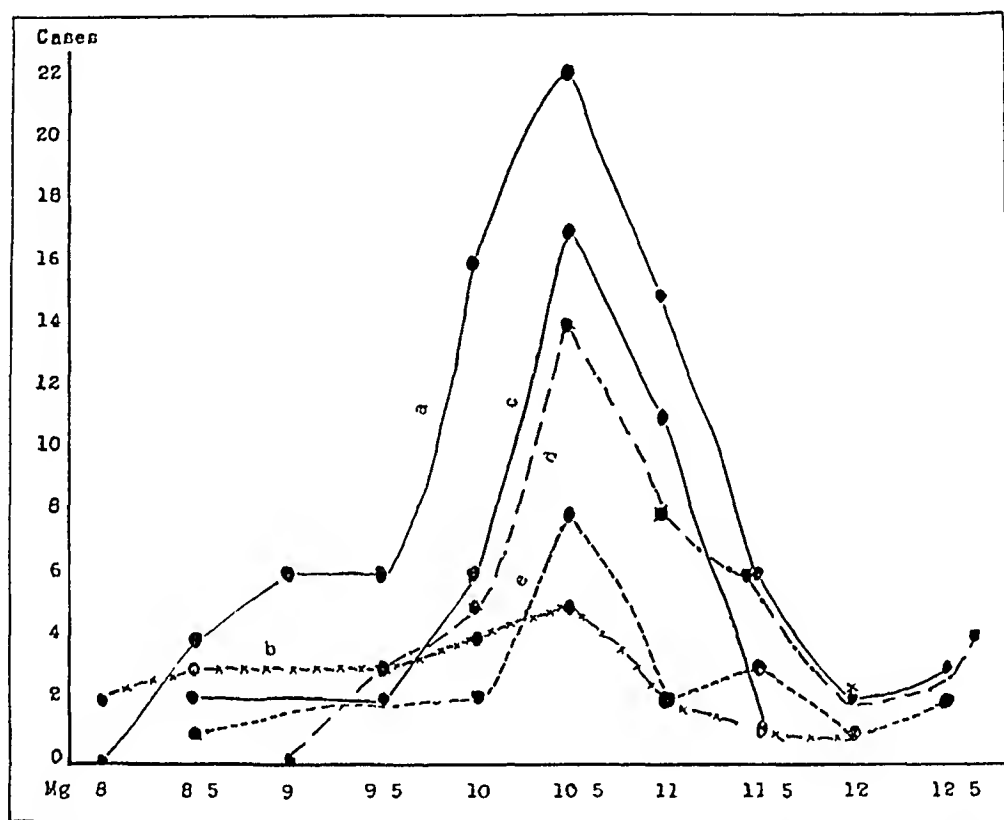
3 Halverson, J. O., Mohler, H. K., and Bergeim, Olaf. The Calcium Content of the Blood Serum in Certain Pathological Conditions, *J. Biol. Chem.* **32**: 171, 1917, Calcium in the Blood in Tuberculosis, *J. A. M. A.* **18**: 1309 (May 5) 1917

4 Schwartz, H. J., and Levin, O. L. The Calcium Content of the Blood in Various Diseases of the Skin Based on an Analysis of over 300 Cases, *Arch. Dermat. & Syph.* **10**: 545 (Nov.) 1924

5 Myers, V. C. Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 170

6 Caven, W. R., and Cantarow, A. *J. Lab. & Clin. Med.* **12**: 1, 1926, abstr. in *J. A. M. A.* **88**: 126 (Jan. 8) 1927

edema The specimens of blood were obtained on a fasting stomach, and the determinations were made according to the technic already mentioned Thus it is found that the values for the asthma group range between 8.5 and 12.5 mg, with an average of 10.08, in the hay-fever group, between 9.3 and 12.3, with an average of 10.55, in the atopic rhinitis group, between 8.3 and 12.2, with an average of 9.95, in the urticaria cases, between 7.9 and 11.4, with an average of 9.66 and in the two cases of angioneurotic edema, an average of 10.4 The average for the entire 167 cases of atopy is 10.19 mg per hundred cubic centimeters of blood, as compared with 10.43 mg, the average value found for the



Blood calcium curve in atopy, *a*, asthma, *b*, urticaria, *c*, normal, *d*, hay-fever, and *e*, atopic rhinitis. The similarity in the general trend of the curves in various atopic conditions as compared with the normal should be noted.

forty normal persons. Moreover, most of the cases studied group themselves, as table 1 and the chart show, within a narrow range. It appears, therefore, that a demonstrable calcium deficiency does not obtain in atopic conditions.

This is not in accord with the work of others. Thus, Novak and Hollander⁷ agree that a calcium deficiency does not exist in asthma and

⁷ Novak, F. J., and Hollander, A. R. Influence of Ultraviolet Irradiation on Calcium Content of Blood Serum in Hay-Fever, Hyperesthetic Rhinitis and Asthma, *J. A. M. A.* **81**: 2003 (Dec. 15) 1923.

in hay-fever, but they find a suggestive lowering in vasomotor rhinitis, their figures ranging from 6.75 to 9.8. Sonnenschein and Pearlman⁸ find an average of 10.9 in the same condition, while Brown,⁹ considering anything below 9.6 mg. as a definite deficiency, finds such a state to exist in a large percentage of practically all forms of atopy.

What is then the status of calcium therapy in atopy? Calcium has been recommended either alone or in conjunction with either thyroid or parathyroid extract and ultraviolet ray exposure, however, little rational, specific basis seems to exist for such therapy. For, in the first place, since the deficiency of calcium had not been proved to exist, why should calcium be administered? Second, calcium lactate in doses of 5 Gm., three times a day, given together with parathyroid extract for twenty days, as table 2 shows, has apparently little if any influence on the blood calcium¹⁰ of atopic patients. Nor does exposure to ultraviolet rays seem to increase

TABLE 2—*Effect of Therapy on Calcium Content of Atopic Blood*

Diagnosis		Blood Calcium Before Therapy	Blood Calcium After Calcium and Parathyroid	Added Ultraviolet Ray Exposure	Therapeutic Improvement
1	Atopic rhinitis	9.7	10.1	10.0	None
2	Atopic rhinitis	11.6	10.1	11.1	Mild
3	Atopic rhinitis	10.4	10.4	10.2	None
4	Atopic rhinitis	10.0	10.2	10.4	None
5	Asthma	9.1	9.2	9.0	None
6	Asthma	10.8	9.7	10.2	None
7	Asthma	11.3	11.0	11.4	Good for 2 months
8	Asthma	10.9	10.6	10.4	None
9	Asthma	9.7	10.3	9.9	None
10	Hay fever	9.9	10.3	10.5	None

the figure, when the subject has a normal blood calcium. At least such an influence could not be demonstrated by the examination of the blood for calcium. It is true that as Kahn and Roe¹¹ have demonstrated, the blood calcium does increase a short time following the administration of calcium lactate, but, like the blood sugar curve, such a rise is not permanent but only transitory. The use of thyroid has been suggested on the assumption¹² that so many of these patients have a low basal metabolic

8 Sonnenschein, Robert, and Pearlman, S. J. Correspondence, *J. A. M. A.* **84** 534 (Feb. 14) 1925, Calcium and Parathyroid Glands in Relation to Hyperesthetic Rhinitis, *J. A. M. A.* **83** 1773 (Dec. 20) 1924.

9 Brown, G. T., and Hunter, O. B. Calcium Deficiency in Asthma, Hay-Fever and Allied Conditions, *Ann. Clin. Med.* **4** 299, 1925.

10 Salvesen, H. A., Hastings, A. B., and McIntosh, J. F. *J. Biol. Chem.* **60** 327 (June) 1924.

11 Kahn, B. S., and Roe, J. H. Calcium Absorption from the Intestinal Tract in Human Subjects. An Experimental Study, *J. A. M. A.* **86** 1761 (June 5) 1926.

12 Novak, F. J. Basal Metabolism in Hyperesthetic Rhinitis, *Wisconsin M. J.* **19** 534, 1921.

rate. A glance at table 3 leads one to suspect with Simpson¹³ and Sonnenschein that the rate is usually either normal or slightly above normal. Only one patient in our series had a basal rate below normal. And this is as one would expect, for clinically these patients are invariably high strung and nervous.

The fact remains, however, that many atopic patients show signs of improvement especially after the intravenous administration of calcium. But in view of the evidence presented, it hardly seems likely that such therapy is on a specific basis. We believe, rather, that what influence is seen is the result of the depressing action which calcium has on all the tissues, especially on the nervous system, as well as because it has a tendency to lessen the permeability of tissue cells and in that way reduce transudation, which is such a common manifestation in the shock organ of atopic persons.¹⁴

TABLE 3—*Basal Metabolic Rate in Atopy*

Number	Name	Diagnosis	Rate	Number	Name	Diagnosis	Rate
1				10	J B	Urticaria	+38
2	J G	Atopic rhinitis	+3	11	A G	Urticaria	+14
3	M M	Atopic rhinitis	+7	12	E T	Urticaria	+29
4	L S	Asthma	+12	13	E M	Urticaria	+10
5	L R	Asthma	+11	14	D J McM	Urticaria	+1
6	E E	Asthma	-10	15	G C	Urticaria	+2
7	M N	Asthma	+14	16	A T	Migraine	+6
8	A L	Asthma	+23	17	M M	Angioneurotic edema	+5
9	E Z	Asthma	+1				

ATOPY AND GASTRIC ANALYSIS

For some time past, we have been impressed with the occasional improvement that is seen in urticaria following the administration of dilute hydrochloric acid. This interest was stimulated further by Beckman¹⁵ who states in a recent report that he has obtained 100 per cent symptomatic cure in a series of seventeen cases of hay-fever by the oral administration of nitrohydrochloric acid. Reference to the older literature reveals that Bishop,¹⁶ Lockard¹⁷ and others have used this drug, and even lemonade, for similar purposes with a great deal of success. It was thought worth while, therefore, to determine whether there is any

13 Simpson, W L. Basal Metabolism in Hyperesthetic Rhinitis and Bronchial Asthma, *Laryngoscope* **32** 768, 1922.

14 New and Nonofficial Remedies, Chicago, A M A Press, 1927, p 109. Editorial. Administration of Calcium Salts, *J A M A* **89** 968 (Sept 17) 1927.

15 Beckman, Harry. Nitrohydrochloric Acid in the Treatment of Hay-Fever, *Am J M Sc* **174** 525, 1927.

16 Bishop, S S. Diseases of Ear, Nose and Throat, Philadelphia, F A Davis Company, 1897.

17 Lockard, L B. The Treatment of Hay-Fever, *Boston M & S J* **148** 59, 1903.

change in the gastric secretion of atopic patients which may suggest the basis for such therapeutic results. This was undertaken not unmindful of the difficulty of interpretation of results of gastric analysis from the standpoint of acidity. For the purpose of control, gastric analysis employing the Rehfuß technic was performed on sixty-five apparently healthy medical students. Of the entire class, there were three cases of achlorhydria, and two of these gave a history of atopy, one of hay-fever and the other of urticaria. Fifty atopic patients were then studied from this standpoint (table 4). The gastric contents were examined in a few cases by the Ewald method and in the rest by the Rehfuß method. Twenty-eight of the fifty patients had asthma, six, urticaria, twelve, hay-fever, two, atopic rhinitis, and one, angioneurotic edema and one, migraine. Nineteen, or 36 per cent, of the entire series, had a complete lack of hydrochloric acid, and four, or 8 per cent, showed complete achylia. Sixteen, or 32 per cent, revealed hypo-acidity, fourteen, or 28 per cent,

TABLE 4—*Gastric Analysis in Atopy*

	Number of Cases Studied	Achylia	Achlor-hydria	Hypo-acidity*	Normal†	Hyper-acidity‡
Asthma	28	2	10	12	12	0
Hay fever	12	0	4	4	4	1
Urticaria	6	2	3	1	3	0
Atopic rhinitis	2	0	1	0	1	0
Angioneurotic edema	1	0	1	0	0	0
Migraine	1	0	0	0	0	1
Total series	50	4	19	17	20	2

* Hypo acidity—any value under 10

† Normal—any value up to 70

‡ Hyper-acidity—any value above 70

were normal and three had hyperacidity. Further examination of table 4 shows that the same is true of the individual conditions considered. This is highly interesting, for a careful search of the literature fails to make mention of such an observation or to explain it. Particularly is it significant because atopic conditions are thought to be associated chiefly with vagotonia, which is closely related to hyperacidity instead of hypo-acidity. These observations are at least suggestive, for it appears that while achlorhydria is not constant in atopy, it is certainly encountered in this condition much more frequently than in normal persons.

CONCLUSIONS

- 1 The normal blood calcium established in our series is 10.43 mg per hundred cubic centimeters of blood.
- 2 A calcium deficiency cannot be shown to exist in atopic conditions.
- 3 Calcium therapy does not seem to produce a permanent increase in the blood calcium of atopically sensitive patients.

4 The basal metabolic rate is not low in these patients, hence, thyroid is contraindicated

Gastric analysis suggests the somewhat frequent presence of an achlorhydria and hypo-acidity in a large percentage of atopic conditions, hence, the advisability of investigating further the effect of acid therapy

1004 May Building

A COMPARISON OF THE EFFECTS OF GENERAL DIETS AND OF STANDARDIZED DIETS ON TOLERANCE FOR DEXTROSE *

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In a previous study ¹ it has been shown that it is possible to change materially a subject's tolerance for dextrose by the use of different types of diet. The different types of diet used to demonstrate this effect were one consisting strictly of protein, one of fats, one of carbohydrates, in another group food was not taken. The subjects of this experiment were normal, healthy, male medical students. They were instructed to follow certain of the dietary outlines mentioned for two days, and on the third morning, on a fasting stomach, a dextrose tolerance test was run on each subject with the use of 1.75 Gm of dextrose per kilogram of body weight. Briefly, the results were the subjects who had consumed only carbohydrates possessed a markedly increased tolerance for dextrose, those who had eaten only proteins showed a mild inability to remove the dextrose from the blood stream, whereas the subjects who had taken fats or who had starved for a period of two days showed a marked decrease in their tolerance for sugar as judged by the clinical dextrose tolerance test.

It was suggested that possibly some of the variability seen in the dextrose tolerance curves in normal persons might be eliminated if a standardized diet was followed for a few days prior to the performance of the dextrose tolerance test. It was further suggested that some of the dextrose tolerance curves believed to be characteristic of certain pathologic disorders might, in reality, be the effect of the diets taken because of the pathologic conditions.

I have attempted to study the effect of a standardized diet on the clinical dextrose tolerance test. Healthy, young, male medical students were again used for the purpose of studying this effect. Their basal requirement in calories was determined, and 25 per cent was added for the moderate activity of these students. The total calories were divided as follows: 0.66 Gm of protein per kilogram of body weight, 2.5 Gm

* From the Departments of Internal Medicine and Physiology, Baylor University, College of Medicine.

¹ Sweeney, J. Shirley. Dietary Factors That Influence the Dextrose Tolerance Test, *Arch Int Med* **40** 818 (Dec.) 1927.

of carbohydrate per kilogram and the remaining calories were supplied in fats. This gave what appeared to be an average balanced tray. The students all felt that it was approximately what they had been eating, except perhaps for a slight deficiency in bread. The students continued on these diets for two days. On the third morning, without breakfast, they reported for a determination of the tolerance for dextrose.

TABLE 1—*Results of Dextrose Tolerance Tests on Students Who Had Been on Standardized Diet for Two Days*

Subject	Blood Sugar Milligram per Hundred Cubic Centimeters			
	Fasting	Thirty Minutes	Sixty Minutes	One-Hundred and Twenty Minutes
1	77	187	133	146
2	80	160	182	100
3	80	270	182	133
4	93	133	87	56
5	87	129	125	53
6	76	121	93	52
7	103	215	133	105
8	76	243	108	78
9	60	145	78	61
10	63	170	113	108
11	71	167	153	158
12	54	121	143	120
13	53	91	59	44
14	71	182	167	133
15	70	153	104	75
16	78	111	125	91
17	77	121	137	103
18	93	98	114	111
19	56	91	82	66
Total average	75	149	145	95
Average of first thirteen subjects	75	160	125	93

One and seventy-five hundredths grams of dextrose was given per kilogram of body weight. Specimens of blood were taken from the vein before the administration of the dextrose and at thirty, sixty and one hundred and twenty minutes following the administration. I made all sugar determinations by the Folin-Wu method.

Twenty-one students were treated in this manner. For controlled studies, an attempt was made to use the same students at a later date and to repeat the tolerance tests without their having followed any particular diet. In this way, it was possible to see the type of curve that a person would have following a standard diet and following an ordinary general diet. It was impossible in every instance to repeat the tolerance tests on the same students. There were, however, thirteen

cases in which I was able to study the effect of controlled and uncontrolled dieting on the tolerance for dextrose in the same students. Although this number is small, the variation noted is so insignificant that it is felt a larger group of observations would not change the results.

In table 1 the results of the dextrose tolerance test are listed for nineteen students who had taken a standardized diet for a period of two days prior to the test. In table 2, the results of the test for eighteen students are given, some of the students are the same as in table 1,

TABLE 2—*Results of Dextrose Tolerance Tests on Students Who Had Been on General or Uncontrolled Diets*

Subject	Blood Sugar Milligram per Hundred Cubic Centimeters			
	Fasting	Thirty Minutes	Sixty Minutes	One-Hundred and Twenty Minutes
1	57	143	125	75
2	59	129	182	108
3	56	129	93	64
4	78	111	91	100
5	83	118	74	56
6	74	112	89	59
7	67	100	108	103
8	63	143	89	50
9	77	129	69	61
10	69	234	107	53
11	63	167	174	133
12	100	133	190	107
13	59	151	68	75
14	83	174	250	111
15	74	133	85	89
16	63	89	90	49
17	71	91	105	82
18	77	100	105	59
Total average	71	133	116	80
Average of first thirteen subjects	70	133	112	80

whose tests were run following undirected eating habits. The figures on the first thirteen students in each table are the results of the dextrose tolerance tests on the same students following the eating of a standardized diet and without any dietary direction. The figures as presented are shown graphically in charts 1 and 2, as composite curves. In chart 1, the composite curves of the students are compared, with and without the effect of standardized dieting. It should be remembered that not all of these students are the same in both cases. In chart 2, the composite curves for thirteen students are shown, identical in both groups, following the taking of standardized diets and following normal dietary habits.

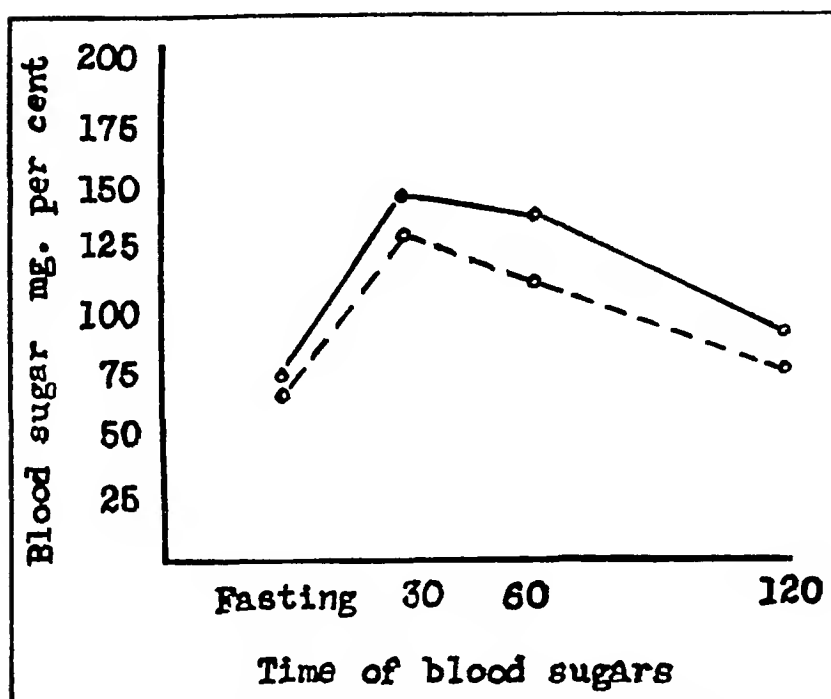


Chart 1—Average or composite curves of the students with and without the effect of standardized dieting The dash line represents those who had taken a general diet

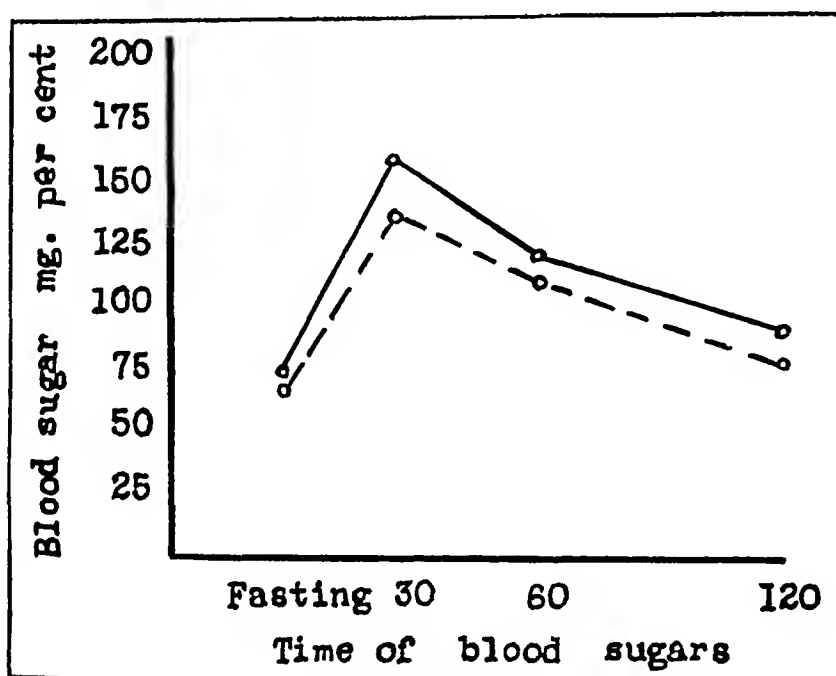


Chart 2—Average or composite curves of thirteen students, identical in both groups, with and without the effect of an antecedent standardized diet The dash line represents those who had taken a general diet

COMMENT

It is not difficult to see that the effect of the preceding diets, as used in this study, is only slight. In chart 1, it will be noted that the curves, although similar in form, might differ significantly quantitatively. This is probably due to the fact that the results for different students were included in these two curves. There is something in a person's metabolic mechanism, regardless of how many variables might be held constant, that causes him to respond in a certain way to dextrose. It will be noted in chart 2, in which the same students are represented in each curve, that the difference is negligible as far as the curves per se are concerned. The slight quantitative difference that exists between the observations is probably to be accounted for by the fact that those who were on the general diets consumed slightly more carbohydrates, which, it is known, will increase a person's tolerance materially, other things being equal. There are no differences noted great enough to allow one to say that an ordinary well mixed general diet in any way distorts one's tolerance to sugars. The suggestion previously made, as alluded to in the beginning, that a standardized diet would perhaps make less variable dextrose tolerance curves, is not borne out. The individual curves included in this study are not plotted because of the requirement of space. Inspection of them, however, or reference to the tables, convinces one that the curves for the thirteen students, on standardized diets, varied just as much as they did for those on an uncontrolled diet.

CONCLUSIONS

Healthy, young, medical students were studied in respect to their tolerance for dextrose, following antecedent standardized or controlled dieting and following uncontrolled dieting. It was found that antecedent standardized diets practically did not have any influence on the variability of the curve for dextrose tolerance as compared to the curves made after the subject had been on an ordinary general diet. There was a slight quantitative difference in the composite curves, which was explained on the basis of the difference in the composition of the diets.

Medical Arts Building

isomeric cycle form has been shown to exist¹ the original conception prevails that urea is largely a waste product excreted almost entirely by the kidneys. The small fraction of ingested urea diverted to other channels is probably more than compensated for by the endogenous quota formed by tissue catabolism.

Speculations regarding a protein sparing function of ingested urea are apparently unsubstantiated by the existing evidence for the irreversibility of urea formation in the body.¹

The importance of these premises is apparent, since the validity of all kidney function tests in which urea is employed, is dependent on their verity.

The idea of estimating renal function, by the rapidity of elimination from the blood of previously ingested urea, is not original. A survey of the literature, however, yielded only two references. One of these is by Archer and Robb,⁵ and the other is a recent one by Rhodebeck,⁶ which appeared in the bulletin of a local hospital.

Rhodebeck failed to obtain results of any practical value. The factor responsible for his observations is discussed in detail subsequently in this paper. At present, it is sufficient to point out that the excessive fluid intake prescribed in his cases produced a diuresis which entailed a secondary increase in the rate of urea elimination from the blood.

Archer and Robb apparently were the first to attempt the estimation of kidney function by a blood urea curve following the ingestion of urea. Unfortunately, the method which they employed was entirely inadequate, since the measurable factor was dominated by incidental variations in blood urea. The bizarre urea values presented by them cast doubt on the accuracy of their micromethod, there was no limitation of fluid intake in their subjects, the period allotted to their test was too short (two hours) to allow the blood urea to return to the control level in normal persons and to permit of proper interpretation of the effects of the ingestion of urea. By following the curve to the rest level as has been done in this series the measurable element is considerably increased and consequently overshadows any chance variations.

CONTROL OBSERVATIONS

The Normal Blood Curve Following Varying Doses of Urea—The results in a small group of normal subjects are indicated in chart 1, which may be summarized as follows:

1. Large doses of urea, 20 Gm. or over, produced an elevation in the blood urea nitrogen reaching a maximum in from two to four

5 Archer, H. E., and Robb, G. D. The Tolerance of the Body for Urea in Health and Disease, *Quart. J. Med.* **18** 274, 1925.

6 Rhodebeck, E. J. Study in Urea Feeding. Preliminary Report, Fifth Avenue Hosp. Clinics, New York, 1927.

hours, depending on the dose. The maximal level obtained was proportional to the amount of urea ingested.

2 The time required for the blood urea to return to the control level similarly appeared dependent on the amount of urea ingested. Because of the prolonged elevations occurring with large doses of urea, the actual time required for the blood urea nitrogen to return to the rest level was not determined, since it appeared probable that these

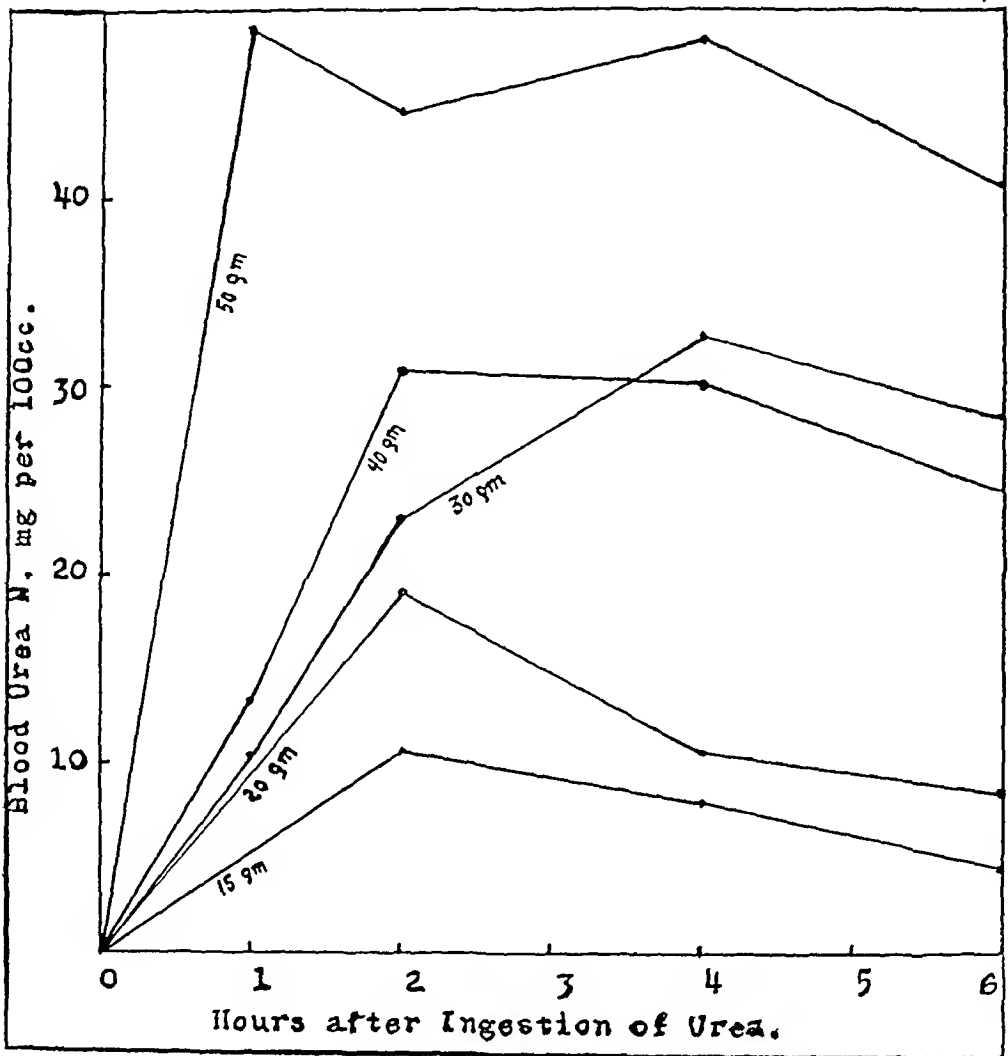


Chart 1—Blood urea curves following graduated doses of urea. The abscissas represent the elevation above rest level.

would persist for longer periods than could reasonably be allotted to the procedure.

The Normal Blood Curve Following 1 Gm of Urea per 10 Pounds of Body Weight—A composite curve using 1 Gm of urea per 10 pounds of body weight, or 15 Gm of urea for an average person weighing 150 pounds (68 Kg), is shown in chart 2. Sixty-five determinations of the blood urea nitrogen in twenty-seven normal cases are plotted

at various intervals following the ingestion of urea. These results may be summarized as follows:

1 Under the conditions of our observations, the ingestion of this amount of urea by normal subjects produced a sharp elevation in the blood occurring between the first and second hour and followed by a gradual fall to the control level within fourteen hours.

2 The maximal elevation usually occurred about the first hour, its extent varying, however, in individual cases. In some cases, elevations as high as 14 or 15 mg of urea nitrogen above the rest level were obtained.

3 The blood urea level at the second hour was subject to less variation. The average elevation above the rest level was 10.1 mg of blood urea nitrogen.

This is of considerable interest, since it checks closely with the results of Marshal and Davis² who calculated that 15 Gm of urea at equilibrium produced a rise of about 10 mg of blood urea nitrogen in a person weighing 150 pounds (70 Kg). Rabinowitch,⁷ incident to a study of the MacLean test, reported an average elevation of 9.5 mg of blood urea nitrogen, two hours following the ingestion of 15 Gm of urea in 200 normal subjects.

The explanation of the fluctuations occurring during the early period of absorption is indicated by the work of Marshal and Davis. Following the intravenous injection of urea into animals, they discovered that the immediate elevation in the blood urea was followed by a rapid fall, which they ascribed to diffusion into the tissues. Eighteen minutes following the injection, equilibrium between blood and tissue had not yet been reached. It is obvious that an even longer period would be necessary to establish equilibrium following oral administration.

In view of the relative constancy in the concentration of blood urea two hours following ingestion, it was concluded that this represented the equilibrium level and was selected as a critical point for comparative observations. At this time, the blood urea concentration is roughly dependent on the body weight, i. e., the amount of tissue available for the diffusion of urea.

Urea diffuses readily into all the tissues excepting bone, fat, cartilage and dermal structures. According to Marshal and Davis,² over 90 per cent of all tissues contain urea. Similarly it diffuses into exudates and edema fluid.⁸ At equilibrium, the concentration of urea in the blood and tissues is identical, with the exception of the tissues mentioned and

7 Rabinowitch, I. M. The Urea Concentration Test, *Arch Int Med* **28** 827 (Dec.) 1921.

8 Dennis, W., and Minot, A. S. The Nonprotein Constituents of Edema Fluids, *Arch Int Med* **23** 879 (Dec.) 1917.

the kidneys, in which the concentration of urea is much higher than in the blood. This does not necessarily indicate storage of urea, since in the chemical analysis of kidney tissue contamination with urine is unavoidable.

Excretion of urea by the kidneys and its distribution throughout the tissues, occurring simultaneously, accounts for the sharp fall which frequently occurs in the blood concentration, from the early maximum.

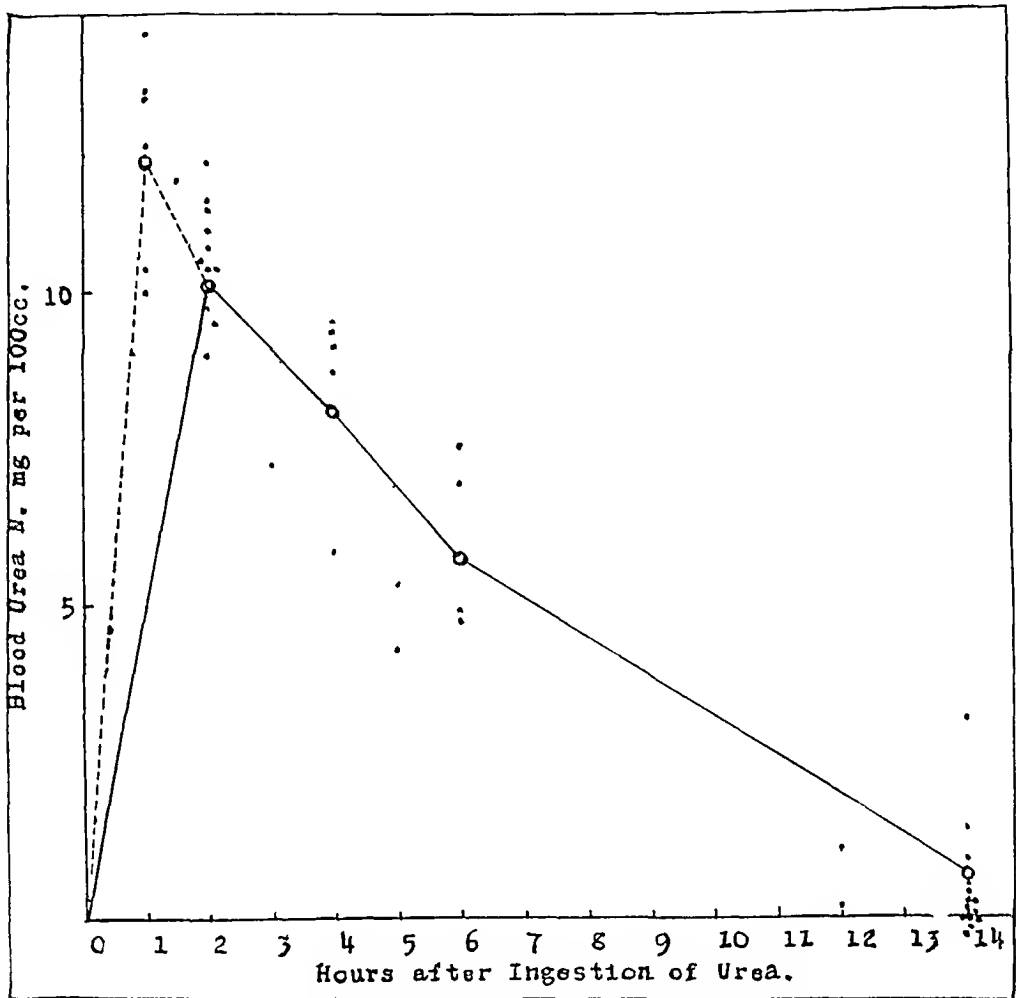


Chart 2—The normal blood urea curve following the ingestion of 1 Gm of urea per 10 pounds of body weight. A composite curve of sixty-five estimations at varying periods after urea ingestion in twenty-seven normal subjects. The abscissas represent the elevation above rest level. The circles indicate average values.

level to the point of equilibrium. The rate of urea excretion is greatest when the concentration of urea in the blood is highest. From 3 to 4 Gm of urea may be excreted in the urine in the first two hours after ingestion. The importance of this factor is indicated by the high levels of blood urea occurring at the point of equilibrium in cases with impaired renal function.

In order to produce a similar rise of 10 mg of blood urea nitrogen two hours after the ingestion of the urea in persons of varying weight, corrections are necessary on the basis of 1 Gm of urea for every 10 pounds deviation from 150 pounds. Thus, a person weighing 120 pounds (54.4 Kg) would require a test dose of 12 Gm of urea, and one weighing 170 pounds (77.1 Kg) would require 17 Gm. Similar adjustments are necessary for edema fluids and effusions. The reason for these corrections is the necessity of producing elevations of blood urea as nearly identical as possible. To obtain comparable results, the response of the kidneys to an identical stimulus must be studied, this being the elevation in the blood urea nitrogen.

The rate of absorption from the gastro-intestinal tract undoubtedly modifies these conclusions. It seemed doubtful whether the elimination of this factor through the intravenous administration of urea would be worth the technical difficulties introduced, and from previous considerations, it appeared improbable that it could be entirely eliminated.

TABLE 1—*Blood Urea Variations Over a Fourteen-Hour Fasting Period*

Case	Mg of Blood Urea Nitrogen per 100 Cc			Kidney Function
	Control	After 14 Hours	Variation	
H	18.1	20.2	+2.1	Normal
B	21.2	18.9	-2.3	Normal
M	14.7	15.2	+0.5	Normal
M	7.0	6.7	-0.3	Normal
R	42.8	40.8	-2.0	Severely impaired

4 In all normal cases, the blood urea nitrogen had fallen within 2 mg of the rest level at the end of fourteen hours. In many cases, the return to rest level occurred even after twelve hours, but since this was not uniformly true, fourteen hours was chosen as the period for observation. Objections to the length of this period, representing one of starvation, were overcome to a great extent by the administration of urea in the evening carrying the test through the sleeping hours.

A few control observations were made to study the normal variation in blood urea occurring over a fourteen-hour fast period. In four normal cases and in one of severe nephritis, the variation between the values at the beginning and at the end of this period did not exceed 2.3 mg of urea nitrogen (table 1).

These results check closely with the observations of MacKay and MacKay,⁹ who found the hourly variation in blood urea nitrogen did not exceed 3 mg in six normal subjects, who were studied over long periods under ordinary conditions. It would be expected that the variations in blood urea would be diminished under the conditions of our

⁹ MacKay, E, and MacKay, L. L. The Concentration of Urea in the Blood of Normal Individuals, *J. Clin. Investigation* 4: 295, 1927.

observations, as the subjects stayed in bed and did not receive any food during the period studied

One gram of urea for each 10 pounds of body weight or 15 Gm for an average adult weighing 150 pounds was chosen as the standard dose for the following reasons

- 1 The period required for the blood urea to return to the control level is considerably shorter than that with larger doses

- 2 Smaller amounts of urea produce an insufficient rise in the blood to be of value in plotting a curve

- 3 This is the dose employed in the MacLean urea concentration test, which could be performed simultaneously, if desired

- 4 Although this amount of urea is ingested without difficulty, larger doses may occasionally produce disturbances of the gastro-intestinal tract

Calculation of the dose of urea in grams and the body weight in pounds may provoke criticism. The utility of this step is obvious, since by so doing, decimal points and fractions are eliminated from the calculations

The Influence of the Volume of Urine on the Excretion of Urea — In the routine adopted in this test, about 500 cc of fluids was permitted, the purpose being to obtain moderate volumes of urine for the fourteen-hour period

The influence of the volume of urine on the rate of excretion of urea has been the subject of considerable investigation since the work of Ambard, Austin, Stillman and Van Slyke¹⁰ concluded that the rate of excretion of urea was proportional to the square root of the volume of urine within certain limits. This mathematical relationship has not been entirely confirmed. Addis¹¹ came to the conclusion that a relationship between the volume of urine and the rate of excretion of urea existed only with oliguria, and that with increasing volumes of urea the rate of excretion of urea was augmented only temporarily. Within certain limits, however, it is agreed that the volume of urine does influence the rate of excretion of urea.

This feature was illustrated by certain observations in a normal subject, who did not take the full amount of fluid allotted and perspired considerably during the course of the test. The volume of urine for the fourteen hour period in this case was only 150 cc. A persistent elevation amounting to 3.6 mg of blood urea nitrogen was present at

10 Austin, Stillman and Van Slyke (footnote 4, third reference)

11 Addis, T., and Watanabe, J. The Effect of Changing the Volume of Urine on the Excretion of Urea, *J Biol Chem* **29** 399, 1917. Addis, T., and Drury, D. R. The Effect of Changes in Urine Volume on the Rate of Urea Excretion, *J Biol Chem* **55** 639, 1923.

the end of the test Repetition of the procedure with provisions for an adequate volume of urine yielded a normal curve (case A F, table 2) The excretion of 15 Gm of urea in 150 cc of urine is apparently beyond the capacity of the normal kidney This would necessitate concentration of urea in the urine of 10 per cent, which Ambard,¹² Addis¹³ and others¹⁴ have shown does not occur even under the most unusual conditions

Case B C, table 2, illustrates the effect of increasing the fluid intake in a patient with slightly impaired kidney function A slight retention in the blood curve initially present disappeared when the volume of urine was increased by the forced ingestion of fluid In case M N (table 2) with kidney function severely impaired, increasing the urine volume from 700 to 1,100 cc markedly diminished the blood urea retention In patients with impaired kidney function, polyuria

TABLE 2—*Influence of the Volume of Urine on the Blood Urea Curve*

Case	Urea Test					Clinical Diagnosis
	Mg of Blood Urea Nitrogen per Hundred Cubic Centimeters				Urine Volume	
	Control	After Urea		Retention		
		2 Hrs	14 Hrs			
A F	13.0	23.9	16.6	3.6	150	Normal
	18.0	.	18.6	0.6	650*	
B O	16.1	29.5	18.6	2.5	500	Nephritis of pregnancy
	17.1	31.0	17.5	0.4	1025*	
M N	20.4	36.0	32.8	12.4	700	Chronic nephritis
	26.9	46.4	34.0	7.1	1100	

* Increased fluid intake

appears to exist as a compensatory mechanism to permit the elimination of urea and other waste products

The proper evaluation of the changes in the blood urea following the ingestion of urea demands that the volume of urine must be within certain limits The optimal volume in this kidney function test is about 500 cc Under such conditions, considerable work is required from the kidney which is forced to excrete urea in concentrations over 3 per cent to prevent retention in the blood Increased fluid intake or even neglect in restricting fluids will normally result in polyuria, owing to the intrinsic diuretic action of the ingested urea Under such con-

12 Ambard (footnote 4, second reference)

13 Addis, T, and Foster, M G The Concentrating Capacity of the Kidneys, Arch Int Med **34** 462 (Oct) 1924

14 Adolph, E F Excretion of Water by the Kidneys, Am J Physiol **65** 419, 1923 Volhard (footnote 3, second reference) Ambard (footnote 4, third reference)

ditions, the capacity of the kidneys to perform work, i. e., to concentrate urea in the urine, cannot be properly studied

Some recent work by Rhodebeck⁶ published during the course of this investigation illustrates the erroneous results that may be obtained if this factor is neglected. He reported similar blood curves following the ingestion of urea by normal persons and in persons with nephritis. His results are readily explained by the conditions of his experiments, in which excessive fluid intake produced a marked polyuria. Under such conditions, urea is eliminated with equal facility by normal and by some impaired kidneys.

THE METHOD OF STUDY

Although slight changes were at first necessary, the following method was subsequently adopted for purposes of uniformity and simplicity.

1. Supper was not usually given on the evening of the test. A meal low in protein content, consisting of fruit or a vegetable salad, taken several hours before the test did not appear to affect the results materially. Moderate restriction of fluid, however, was found to be essential.

2. In the evening at the beginning of the test, the patient voided, and the specimen was discarded. He was then instructed to collect all urine until the test was completed.

3. At this time, an oxalated specimen of blood was collected.

4. The patient was then given 1 Gm. of urea for each 10 pounds of body weight, i. e., 15 Gm. for an adult weighing 150 pounds. Crystalline urea was dissolved in about 8 ounces of well sweetened lemonade. It was found that urea is best taken in such a vehicle. Tea and coffee were avoided because of their diuretic action. It is necessarily essential to insure the complete ingestion of the urea. If vomiting occurred, the test was abandoned. This, however, took place only once in our series.

5. Two hours following the ingestion of urea, a second specimen of blood was collected. When inconvenient, this specimen was omitted without materially affecting the interpretation of the test.

6. To insure both ease of supervision and to diminish metabolism, the patient stayed in bed during the entire period of observation. Since this occurred at night, it was not found irksome.

7. The following morning, fourteen hours after the ingestion of urea, the last specimen of blood was taken. At this time, the volume of urine was measured, thus completing the test.

This method was found simple in execution and interfered little with hospital routine or the comfort of the patient. The omission of

the second specimen of blood permitted the use of this test in some cases in the outpatient department

The method used for the estimation of blood urea nitrogen is the one described by Myers¹⁵

INTERPRETATION

1 It was found that for all practical purposes, the concentration of blood urea at the second hour yielded relatively minor information, except that it indicated adequate absorption of urea. Although in patients with severely impaired kidney function the elevation was usually of greater extent than in the normal person, this varied even in the same person.

2 The elevation of blood urea nitrogen persisting above the rest level fourteen hours after the ingestion of urea was employed as the basis of interpretation of this test.

Variations up to 2 mg of blood urea nitrogen above the control level were considered within normal limits, providing the output of urine was not excessive.

3 Under the conditions of this procedure in which excessive intake of fluid was prohibited, a urine volume of over 750 cc for the fourteen-hour period was considered abnormal.

CLINICAL APPLICATION

It is generally recognized that for most practical purposes the fasting blood urea is a good index of kidney function. MacKay and MacKay¹⁶ have recently shown that an increase in fasting blood urea does not occur until over 50 per cent of the kidney structure has been destroyed. When kidney function is grossly impaired as indicated by the functional tests in common use, any new modification or procedure is superfluous. It is only in the larger group of cases in which insidious pathologic changes of the kidneys are present, which are not indicated by casual examination, that a new test may be of value.

There are too many unknown variable factors influencing the function of the kidneys for the results of any test to be strictly quantitative in character. It is not claimed that the degree of retention of urea strictly parallels the extent of pathologic change in the kidneys. That function and structure are not always parallel is generally recognized. The purpose has been to determine if minor degrees of impaired kidney function could be detected which under ordinary condi-

15 Myers, V. C. *Practical Chemical Analysis of the Blood*, St. Louis, C. V. Mosby Company, 1924, p. 45.

16 MacKay, E., and MacKay, L. L. The Relation Between the Blood Urea Concentration and the Amount of Functioning Renal Tissue, *J. Clin. Investigation* 4: 127, 1927.

tions escape observation. By subjecting the kidney to the necessity of eliminating a relatively large amount of urea in a limited volume of urine, conditions of strain are produced to which only a perfectly functioning kidney can respond normally. It has been previously shown that if these conditions be made still more severe by further decreasing the urine volume even the normal kidney becomes inadequate to the task of complete elimination of the additional urea in the given time.

The material in this study was divided into three groups from the point of view of renal function: a normal group, one in which renal function was definitely impaired, and a third in which impairment

TABLE 3—*Urea Test in Patients with Definitely Impaired Kidney Functions*^{*}

Case	Blood† Urea Nitrogen Mg 100 Cc	Urea Test					Urine Volume in Cc 14 Hrs	Clinical Diagnosis
		Mg. of Blood Urea Nitrogen per Hundred Cubic Centimeters						
		Control	After Urea		Reten- tion			
			2 Hrs	14 Hrs				
A P	20.4	20.4	38.7	36.3	15.9	610	Chronic diffuse nephritis	
J R	55.6	47.1	63.4	61.0	13.9	700	Chronic nephritis	
O G	18.0	18.6	31.8	27.9	9.3	400	Syphilis, amyloidosis	
M G	11.7	11.5	27.4	20.7	9.2	800	Bilateral cystic kidney †	
J P	32.5	25.9	35.0	31.2	5.3	1200	Pyelonephritis, chronic nephritis §	
P A	38.4	26.0	39.4	35.1	9.1	900	Paralysis of bladder, tumor of the cord †	
E K	34.8	20.1	34.4	27.6	7.5	1500	Calculus in renal pelvis, pernicious anemia †	
J L	12.6	9.8	21.0	18.4	8.6	1050	Chronic nephritis	
M N	19.7	20.4	26.0	32.8	12.4	700	Chronic nephritis §	
J M	26.2	22.5	35.0	29.3	6.8	1120	Chronic nephritis	
A D	75.0	70.2	82.6	85.0	14.8	400	Chronic nephritis, uremia §	
I W	54.8	53.3	91.6	99.3	16.0	200	Chronic nephritis, uremia	
L D	18.4	17.0	31.8	24.0	6.1	1100	Cerebrospinal syphilis, paralysis of bladder †	
A F	19.4	25.0	44.0	32.1	7.1	700	Pyelonephritis	
J B	14.2	12.3		23.6	11.6	400	Acute nephritis	
F B	12.0	10.7	22.2	15.7	5.0	480	Pernicious anemia	

* Protein, casts or cells were present in the urine in all cases. The two hour and phenol-sulphonphthalein test were impaired in all cases.

† On admission.

‡ Confirmed by exploratory operation.

§ Confirmed by tissue examination.

of renal function was suspected. The clinical observations, the routine examination of the urine, the fasting blood urea, uric acid and creatinine, the two-hour test, the phenolsulphonphthalein test and occasionally the MacLean test were used as the basis for classification. The results in the normal group have already been discussed.

The Blood Urea Curve in Patients with Definitely Impaired Renal Function—The changes occurring in the blood urea in a group of sixteen patients with definitely impaired renal function are indicated in table 3 and chart 3. These patients showed evidence of a pathologic processes in the kidneys, indicated by large amounts of urinary protein, red blood cells or casts. In half of this group, initially elevated blood urea, uric acid and creatinine values were present. Impairment of renal function was evident by the abnormal two-hour tests and the diminished

excretion of phenolsulphonphthalein. The initially low blood urea values in some were deceptive, since they were attributable to previous prolonged protein restriction. In several of this group, the diagnosis was subsequently confirmed by autopsy. The results may be summarized as follows:

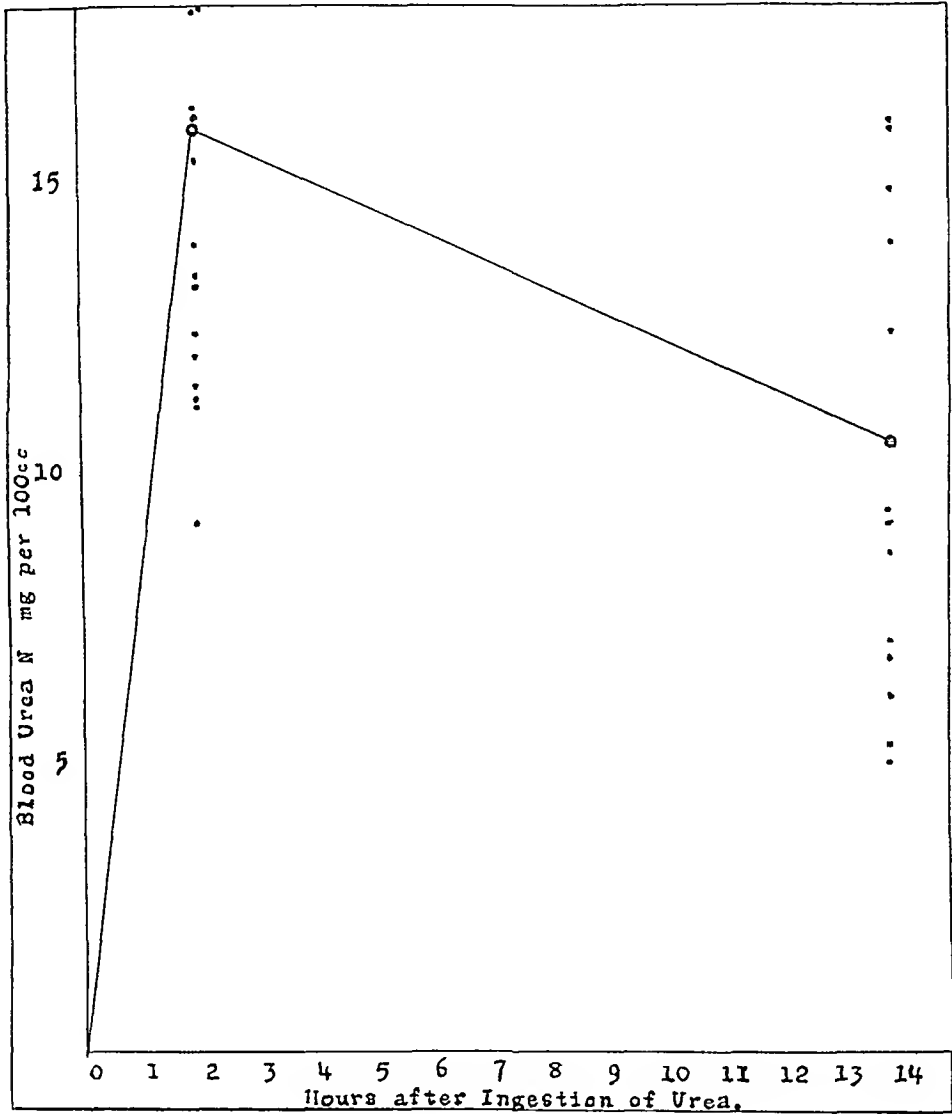


Chart 3—The blood urea curve with kidney function severely impaired. A composite curve of sixteen cases with advanced renal functional impairment following the ingestion of 1 Gm of urea per ten pounds of body weight. The abscissas represent the elevations above rest level. The circles indicate average values.

1. The blood urea, two hours following the ingestion of urea, was definitely higher than normal. The average elevation in terms of blood urea nitrogen was 15.9, contrasted with a normal average of 10.5. Individual elevations of over 18 mg were obtained.

2 After fourteen hours, there remained an average residual elevation of 10.3 mg above the control level. Consequently, on the average, less than one third of the urea given had disappeared from the blood.

3 In about half of these cases, a marked polyuria, over 750 cc, was present for the fourteen-hour period in addition to the abnormal blood curve.

4 In two cases of uremia, the blood urea continued to rise during the fourteen hours. Apparently, the kidneys were unable to eliminate not only the urea administered, but also that produced by catabolism of the tissues, which is known to be increased in this condition.¹⁷ Another interesting feature was the loss of the compensatory polyuria, which was replaced by a relative oliguria in these two cases.

It is to be noted that in none of these patients who were severely ill did the ingestion of urea produce any discomfort or influence their clinical condition in any way.

The Blood Urea Curve in Patients in Whom Impairment of Renal Function was Suspected—A third group of patients were studied in whom pathologic processes seemed present in the kidneys, and some impairment of renal function was suspected but not confirmed by the usual methods. The basis for selection of these patients was the presence of moderate to large amounts of protein, casts and red blood cells in the urine, with normal contents of the blood and normal, two hour and phenolsulphonphthalein tests. Included in this group were some patients in whom it is clinically recognized that depression of renal function may occur. The group consisted of cases of acute glomerular nephritis, early cases of chronic diffuse nephritis, nephrosis, infections and obstructive lesions of the urinary tract, chronic passive congestion due to cardiac disease and some cases of jaundice and severe anemia. The results in this group indicated in table 4, are classified under their clinical subdivisions.

Primary Renal Disease Moderate retention of urea above the test level after fourteen hours occurred in cases of acute nephritis, chronic nephritis, primary contracted kidneys and various infections and obstructions of the urinary tract. Even in early renal disease, such as in mild subsiding glomerular nephritis, nephrosis and minor infections of the urinary tract, the retention of urea though less marked was unmistakable. In some of these cases, diminished function was also made evident by a marked fourteen-hour polyuria.

Cardiac Disease In the well compensated stage of cardiac disease, a normal response was obtained, and this was true even in some cases with edema. The fixation of the two hour test at a high level which is usual in these cases is probably dependent on disturbed excretion of

¹⁷ Mosenthal, H. O. *Metabolism in Nephritis*. Endocrinology and Metabolism, vol. 4, New York, D. Appleton & Company, 1922, p. 337.

salt and water, which at first does not influence the elimination of nitrogen as long as the volume of urine is adequate. In one case, that of A S (table 4), retention of urea was noted during the stage of marked chronic passive congestion, subsequently a normal reaction to the test occurred when the efficiency of the circulation had been restored. That this retention was probably due to an actual disturbance in renal

TABLE 4—Urea Test in Patients in Whom Impairment of Kidney Function was Suspected*

Case	Blood† Urea Nitrogen Mg 100 Cc	Urea Test					Urine Volume in Cc 14 Hrs	Clinical Diagnosis
		Mg of Blood Urea Nitrogen per Hundred Cubic Centimeters						
		Control	After Urea		Reten- tion			
			2 Hrs	14 Hrs				
T O	15.6	22.2	34.3	30.5	8.3	500	Chronic nephritis	
M W	17.9	12.8	27.4	21.4	8.6	650	Acute nephritis	
L K	19.7	21.4	28.8	25.0	3.6	450	Chronic nephritis	
M H	16.6	18.0	40.0	28.4	10.4	900	Chronic nephritis, hypertension	
H G	12.4	15.3	29.4	22.8	7.5	400	Tuberculosis of kidney	
L M	29.8	12.3	26.7	19.8	7.5	600	Chronic nephritis, cardiac decom- pensation	
M H	10.5	10.5		15.3	4.8	620	Pyelonephritis	
R G	11.6	11.1	22.6	17.5	6.4	520	Renal tuberculosis	
G K	11.7	12.1	21.6	16.8	4.7	450	Cystitis and pyelitis	
A B	20.8	20.2	32.6	22.4	2.2	1400	Large renal calculus	
C M	9.9	10.2	19.7	11.8	1.6	800	Pyelitis	
M B	11.9	10.5	20.0	13.5	3.0	500	Pulmonary Tuberculosis, nephrosis	
M P	28.0	15.2	34.4	20.4	5.2		Renal calculus, multiple abscesses of kidney	
I M	11.1	10.0	17.3	10.3	3	1800	Hydronephrosis	
H E	11.3	11.3		14.4	3.1	500	Albuminuria	
B C		16.1	29.5	18.6	2.5	500	Toxemia of pregnancy, hyperten- sion	
D F	18.4	17.2		20.6	3.4		Jaundice, cholecystitis	
E D	22.0	22.9	36.0	29.8	6.9	500	Jaundice, ascites, syphilis of liver	
A D	9.7	13.6	21.6	17.0	3.4	1400	Jaundice, hepatitis, renal calculus	
A S	15.2	14.0	31.6	21.4	7.4	700	Cardiac decompensation, with ascites and edema	
A S	14.6	12.2	19.8	12.5	3	680	Cardiac, same case, compensated, no edema	
M L	16.6	13.4	26.0	17.3	3.9	400	Jaundice, cardiac decompensation	
G R	12.4	21.0		24.4	3.4	400	Jaundice, cancer of the liver	
M T	10.5	8.9	16.4	13.6	4.7	600	Jaundice, severe anemia	
N B	18.4	9.1	21.0	14.5	5.4	600	Pernicious anemia	
W T	12.8	9.7	20.6	13.3	3.6	380	Pernicious anemia	
P C	10.0	13.5		15.4	1.9		Hypertension	
A S	12.1	18.6		19.0	4	550	Essential hypertension	
B Z	12.2	11.0		11.0	0	650	Hypertension, previous nephrect- omy	
J M	18.0	15.9		16.4	5		Essential hypertension, aortitis	
J W		9.0		9.9	9	450	Essential hypertension	

* The two hour and phenolsulphonphthalein tests were normal in all cases. Protein, cells or casts were present in the urine in all cases.

† On admission.

function dependent on disturbed circulation rather than to oliguria was evidenced by the adequate volume of urine, of 700 cc originally present during the fourteen-hour period. It is obvious that urea retention can occur in cases of chronic passive congestion with marked oliguria or anuria.

Essential Hypertension In the absence of nephritis or contracted kidney, neither abnormal retention of urea nor polyuria occurred in five cases studied.

Jaundice The occurrence of renal irritation incident to prolonged jaundice is generally recognized¹⁸ Protein and casts are frequently present in the urine in this condition In several cases of hepatic disease with jaundice and ascites, moderate retention of urea occurred (cases D F, E D, M L, G R and M T, table 4) It seems hazardous to conclude that this indicates purely renal impairment, since the influence of the liver on urea metabolism is still poorly understood

Anemia The occurrence of impaired kidney function in pernicious anemia was first pointed out by Mosenthal¹⁹ in a study of the two hour test, and subsequently by Christian²⁰ The frequency of a mild pathologic process of the kidneys in this condition has recently been emphasized by Stieglitz²¹ In four cases of pernicious anemia, moderate retention of urea occurred in the blood following the ingestion of urea Retention did not occur in several cases of secondary anemia

The miscellaneous character of the remaining cases does not permit of any further clinical classification

COMMENT

The purpose of this investigation has been to ascertain whether renal function can accurately be gaged by the capacity of the kidney to excrete large amounts of urea under special conditions This has been done by a study of the changes occurring in the concentration of blood urea following the ingestion of 15 Gm of urea for an adult weighing 150 pounds or the equivalent by weight An important element in this procedure is the limitation in urinary volume to about 500 for the fourteen hour period when possible Under these conditions the results obtained show a degree of sensitivity comparing favorably with most kidney function tests

Objections may arise to the assumption of measuring renal function as a whole, by the capacity to eliminate urea "It is generally recognized that the kidney does not accomplish work as a unit, but that in forming urine, it eliminates salt, water, uric acid, and urea, by processes which to a certain extent are independent of one another"²² Thus Myers, Fine

18 McCrae in Osler Modern Medicine, vol 3, Philadelphia, Lea & Febiger, 1926

19 Mosenthal, H O Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen and the Specific Gravity of the Urine, Arch Int Med **16** 733 (Nov) 1915

20 Christian, H A Renal Function in Anemia, Arch Int Med **18**:429 (Oct) 1916

21 Stieglitz, E J Disturbances of Renal Function in Pernicious Anemia, Arch Int Med **33**:58 (Jan) 1924

22 Mosenthal, H O The Value of Tests for Renal Function in Clinical Medicine, Ohio State M J **18** 348 (May) 1922

and Lough²³ found that in the early stages of impaired renal function uric acid retention preceded that of urea in the blood. Although many functions are performed by the kidney, it is probable that the elimination of nitrogen is one of the most fundamental and the earliest impaired. Recently it has been recognized that in nephrosis and possibly in chronic passive congestion, the retention of water and salt occurs primarily in the body,²⁴ and that no essential impairment of kidney function is present. DeWesslow²⁵ has shown that in the absence of edema, the excretion of sodium chloride and nitrogen is strictly parallel, and that both are retained to a like degree in chronic nephritis, while Denis²⁶ and Loeb and Benedict²⁷ reported a similar relationship between sulphate and nitrogen.

CONCLUSIONS

1 Following the ingestion of 1 Gm of urea per 10 pounds of body weight, a characteristic normal curve of blood urea was obtained. The blood urea returned to the control level in fourteen hours.

2 Under similar conditions, a radically different curve was obtained in cases of impaired kidney function. Deviation from the normal occurred even in the early stages of renal impairment. With severely impaired renal function, the deviation from the normal was marked.

3 Early degrees of renal impairment were frequently indicated by marked fourteen hour polyuria (over 750 cc), although the blood curve remained normal.

4 Based on these results, a simple test of kidney function is described, and the clinical applications are discussed.

23 Myers, V. C., Fine, M. S., and Lough, W. G. The Significance of the Uric Acid, Urea and Creatinin in Nephritis, *Arch. Int. Med.* **17**: 570 (April) 1916.

24 Fishberg, A. M. The Unitary Nature of Impairment of Renal Function, *Arch. Int. Med.* **38**: 259 (Aug.) 1926. Aldrich, C. A. A study of the Clinical Course of Generalized Edema, *J. A. M. A.* **84**: 481 (Feb. 14) 1925.

25 DeWesslow, O. L. V. The Excretion of Chlorides by the Healthy and Diseased Kidney, *Quart. J. Med.* **19**: 53 (Oct.) 1925.

26 Denis, W. Sulphates in the Blood, *J. Biol. Chem.* **49**: 311, 1921.

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AGRANULOCYTOSIS (SCHULTZ) AND THE AGRANULOCYTIC SYMPTOM COMPLEX *

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In 1922, Schultz¹ described a series of cases of a peculiar type of necrosing angina accompanied by a marked absolute and especially granulocytic leukopenia. He asserted that these symptoms were manifestations of a specific disease which he called "agranulocytosis." Since that time, numerous reports of similar cases, at present about 125, have appeared in the literature designated as agranulocytosis or agranulocytic angina (Friedemann²). The results of an investigation of 5 cases of agranulocytosis observed between November, 1927, and April, 1928, and a careful and critical study of a large number of records of agranulocytoses induced me to present a discussion of the symptomatology, pathology and differential diagnosis of this disease, because, in my opinion, the term "agranulocytosis" is in a number of cases applied to conditions which differ distinctly from those for which Schultz introduced this name. The following description of the clinical and pathologic aspects of the disease was obtained after the exclusion of all those cases which could not be definitely classified among the essential agranulocytoses.

SYMPTOMATOLOGY

Previous diseases, especially those of the throat, apparently do not have any causative significance. In one case, a commotio cerebri preceded the onset of the disease by several days, and in two cases the patients were under treatment for syphilis. Either the agranulocytosis starts after a more or less protracted period of ill health during which the patients complain that they become easily tired, feel weak and suffer from frequent headache, or, more frequently, it suddenly occurs while the patients are in full health. The symptoms at the onset are high fever of the continued type (from 102 to 104 F), a pulse of

¹ From the Department of Pathology, Loyola University School of Medicine, and the Laboratories of Mercy Hospital.

¹ Schultz Ueber eigenartige Halserkrankungen, Deutsche med Wchnschr **48** 1495, 1922. Schultz and Mirisch Zur Frage der Anginen mit reaktiver Vermehrung Lymphoider Zellen im Blut, Virchows Arch f path Anat **264** 760, 1927. Schultz Seltene Anginaformen und ihre Behandlung, Klin Wchnschr **6** 2437, 1927, Zur Frage der Anginen mit atypischem Verlauf, Deutsche med Wchnschr **53** 1213, 1927.

² Friedemann Ueber Angina agranulocytica, Ztschr f Hals-, Nasen- u Ohrenh **13** 473, 1926.

high rate and bad quality (from 110 to 140), general malaise, dysphagia and dyspnea. One or several chills may precede or accompany these symptoms. The sore throat makes its appearance at the start or during the first three or four days. A rash, herpes labialis, vomiting and pains in the hypogastric region may occur, but are not common. During the course of the disease, the development of a slight, rarely intense jaundice may take place (in about 50 per cent of the cases reported). Diarrhea also may set in during this stage, but it is a less frequent symptom. The patient usually grows worse rapidly, and death results after coma of from two to seven days' duration in most of the cases. A more chronic course, lasting several weeks, occurs less frequently. Remissions of from a few days sometimes to several weeks may rarely occur. The outcome of the disease is in general fatal. Recoveries are recorded in only a few instances (six). Physical examination shows the following. In the beginning, the tonsils are enlarged and reddened and show white or yellowish plugs. These soon merge to dirty gray or yellow coats, on removal of which an ulcerated surface appears. In the progress of the disease, the tonsillar tissue may become greenish black, and the gangrenous material may slough, sometimes leaving only small stumps of the tonsils. Similar necrosing processes may be found on the pillars, uvula, palate, base of the tongue, pharynx or gums, representing either extensions of the tonsillar alterations or independent processes. Stomatitis is frequently present, and an offensive foetor ex ore is always noticeable. The tongue is usually coated. Hemorrhages from the ulcers or underneath the mucosa rarely occur. The submaxillary and cervical lymph nodes are enlarged and tender. The heart is generally normal, except for increased activity. The blood pressure may be somewhat lowered. In the beginning examination of the lungs gives negative results, but later a condition similar to that present in bronchopneumonia may be noticed. Palpation of the abdomen sometimes reveals tenderness in the epigastric region, especially over the gallbladder. The liver and the spleen, the latter more often than the former, are frequently enlarged. Ulcerations similar in appearance to those in the mouth may be observed in the anal region and at the vulva, vagina and uterine cervix. Tests for hemorrhagic diathesis (Rumpel-Leede) give negative results. Petechial hemorrhages in the skin are rare and scanty. Examination of the urine for albumin always gives slightly positive results. The sediment shows hyaline and granular casts, leukocytes and erythrocytes. Ehrlich's test and the test for sugar are negative. Urobilin and urobilinogen may be present in the patients who have jaundice. The bacteriologic examination of the throat does not render results of any special significance. Staphylococci, streptococci and pneumococci are the micro-organisms usually found. Fusospirillosis was noted in about 10 per cent of the cases. The most important observations are made during examination of the blood.

There is a considerable decrease in the number of the leukocytes, which becomes more and more marked toward death (from 1,500 to 100 in 1 c mm.) The granulocytic cells evidently decrease first and may finally disappear completely. Immature forms of these cells are not present, but degenerative forms may be observed. Besides the absolute granulocytic leukopenia, there is also a lymphocytic decrease which follows closely that of the granulocytic cells. The monocytes are sometimes temporarily somewhat increased in number. The oxydase reaction is always negative for these cells. The red blood cell picture (erythrocytes and hemoglobin) is normal or shows only minor changes. The number of the thrombocytes is either normal or increased. Pathologically, large forms are not rarely observed. The coagulation time and bleeding time are normal. The Widal test and the Wassermann test are negative, except in patients previously infected with the corresponding diseases. Blood cultures are more likely to be negative than positive (in about 10 per cent). Different bacteria may be obtained on culture (hemolytic and nonhemolytic streptococci and staphylococci, *Streptococcus viridans*, *Bacillus pyocyaneus*, *Bacillus acidilactici* and *Bacillus coli*). Positive cultures are rarely obtained during the first days of the disease.

PATHOLOGY

The necrosing processes in the mouth may vary considerably. Only a few superficial ulcerations may be present on the tonsils, or there may be extensive, multiple, deep gangrenous destructions involving the esophagus and the larynx. They are sometimes surrounded by a zone that is a wine red in color. Microscopically, the bottom of the ulcers is composed of three layers. A necrotic, granular material intermingled with numerous bacteria forms the uppermost layer. In the next one underneath, which usually extends into the muscle tissue, the tissue is also necrotic but the cellular outlines are preserved. Streaklike accumulations of bacteria may be found in the intercellular spaces. The vessels in this region are thrombotic and contain hyaline or fibrinous material or clotted blood in which the absence of leukocytes is striking. In the still deeper edematous layer, areas of living and necrotic tissue alternate. Smaller and larger accumulations of lymphocytes and plasma cells may be present in varying number.

Subpleural hemorrhages are frequently observed. A fibrinous exudate may cover the pleura in places in which dark red, solid, irregular small foci are present in the lung. Such areas are regularly found, especially in the lower lobes which, moreover, may show hypostatic hyperemia. The capillaries of these solidified parts are hyperemic, the alveoli are filled with red blood corpuscles and in places with bacterial masses. The adjacent alveoli contain an albuminous or fibrinous material. The absence of leukocytes in these foci is remarkable.

Subpericardial and subendocardial hemorrhages are frequently seen

Ulcerations similar to those found in the mouth are frequently present in some or all parts of the digestive tract, especially in the esophagus and intestine, where they are sometimes extensive. The intestinal lymph follicles are swollen, and the mucosa covering the Peyer's patches may be found ulcerated, as in typhoid fever. The stomach shows hemorrhages and erosions more frequently than small single or multiple ulcers.

The liver is usually slightly enlarged and shows evidence of cloudy swelling. Microscopically, varying degrees of fatty degeneration, occasionally multiple focal necroses and in general, an increase and proliferation of Kupffer's cells exist. The bile capillaries frequently contain bile casts and the liver cells bile pigment. Interstitial lymphocytic infiltrations are sometimes observed in scanty to moderate number.

A minor swelling of the spleen is common. It is dark red and moderately firm, but never soft as in septicemia. The lymph follicles are not prominent on the cut surface. The sinuses are well filled with erythrocytes and proliferated reticulo-endothelial cells and lymphoid cells. Cells positive for oxydase are in general completely absent or are only scantily present. Hemosiderin is often found in large phagocytic cells. The lymph follicles are small and atrophic, especially the germinal centers, which are sometimes composed of mature lymphocytes. The proliferated reticulo-endothelial cells may outnumber the lymphoid cells in the spleen. Small anemic necroses are rarely observed.

The submaxillary, cervical, peribronchial and mesenteric lymph nodes are in general enlarged. They may occasionally contain hemorrhages. The microscopic examination reveals atrophy of the lymph follicles as in the spleen and a proliferation of the reticulo-endothelial cells.

The kidneys usually show signs of cloudy swelling. Numerous red points the size of a pinhead are found beneath the capsule in the cortex, they represent swollen, hyperemic glomeruli. On the cut surface, the cortex and medulla are not well demarcated. The tubular epithelium is in general markedly degenerated, and the tubular lumina are frequently filled with casts. Petechial hemorrhages are rarely found in the renal pelvis.

The marrow in the femur is either completely or partly composed of red marrow. It is mainly made up of lymphoid cells. Erythroblasts and megakaryocytes are present in normal numbers. Cells positive for oxydase are rarely seen, and then they are only scanty.

Ulcerations of the same appearance as those described for other organs are frequently observed on the vulva, vagina and cervix. Sometimes, an intra-uterine hemorrhage is present.

GENERAL ASPECTS

Agranulocytosis is by far more frequent in women than in men. According to my investigations, the ratio is 3.5:1. The disease affects mainly those of middle age (from 30 to 50), but occurs also in younger and in older persons. If correct conclusions can be drawn from the origin of the reports, the disease seems to be prevalent in Germany and Austria. The country next in frequency is the United States, with Canada next. Single cases are described by Dutch, French and Italian authors. A reason for this peculiar local distribution is not evident, and suggestions cannot be offered. The disease is apparently not contagious.

THERAPY

Diphtheria antitoxin, arsphenamine locally and intravenously, methenamine, mercurochrome-220 soluble, an organic iodine compound—casein, alcohol, various silver compounds, and acridine dyes and many other local caustics and disinfectants were used without any favorable effects. Temporary improvement was seen after repeated transfusions of large amounts of blood and recovery after administration of polyvalent antistreptococcus serum and roentgen-ray irradiation of the long bones with stimulating doses. The spleen was irradiated without success.

ETIOLOGY

The cause of "agranulocytosis (Schultz)" is still unknown. The theories concerning its etiology as supported by the different authors may be classified into three groups:

1. Friedemann² asserted that it is the result of an endocrine disturbance.

2. Mouzon³ and Roch and Mozer⁴ were inclined to place it in relation to the acute leukemias.

3. The majority of the workers in this subject assert that it is an infectious disease and represents a septicemia with an atypical reaction of the hematopoietic system (Feer,⁵ Weiss⁶) due either to bacteria with a special affinity and toxicity to the granulocytic

3. Mouzon. Agranulocytose, *Presse méd* **34** 1269, 1926.

4. Roch and Mozer. Angina agranulocytotica, *Presse méd* **34** 1171, 1926.

5. Feer. Beitrag zur Frage der Agranulocytose, *Schweiz med Wchnschr* **56** 551, 1926.

6. Weiss. Ueber die gegenseitigen Beziehungen zwischen Schultz'schem Symptomkomplex (Mucositis necroticans agranulocytica), akuter Leukämie und septischem Infekt, *Wien Arch f inn Med* **14** 303, 1927.

system (Zadek,⁷ David,⁸ Sternberg,⁸ Pelnar⁹) or to an atrophy or hypoplasia of this organ because of the presence of a septic infection (Zikovsky,¹⁰ Turk¹¹) According to these investigators, the bacterial cause is either nonspecific (Ehrmann and Preuss¹²) or specific (streptococci [Zikovsky], *Bacillus pyocyaneus* [Lovett¹³] fusospirillosis [Cannon¹⁴]) Schultz¹ and Reye and Wohlwill¹⁵ simply stated that they consider it a disease sui generis and supported their standpoint by emphasizing the uniformity of the pathologic symptoms

DIFFERENTIAL DIAGNOSIS

Numerous diseases may more or less resemble agranulocytosis in one or the other stage They may be classified as follows

1 Diseases showing the agranulocytic symptom complex and necrosing processes in the mouth

(a) Influenza and typhoid fever differ from essential agranulocytosis in their course and their bacteriologic and pathologic manifestations in spite of the existence of a certain resemblance in acute cases in the beginning

(b) Septicemia and its special modifications, such as Werlhof's disease, differ from agranulocytosis in the presence of a general hemorrhagic diathesis, abscesses, a primary infectious focus, immature forms of granulocytes in the blood, thrombopenia, secondary anemia, frequently positive blood culture, hyperleukocytosis in the spleen, fat marrow in the long bones, and myeloid proliferations in the bone marrow

(c) Acute leukopenic leukemias and aleukemic leukemias can be distinguished from agranulocytosis by the existence of a generalized hemorrhagic diathesis, secondary anemia, thrombopenia, lengthened bleeding time, tenderness of the lower part of the sternum and charac-

7 Zadek Zur Frage der "Agranulocytose," Med Klin **21** 688, 1925

8 Quoted by Zadek (footnote 7)

9 Pelnar Malignant Leukopenia, Čas lek česk **63** 1653, 1924, abstr, J A M A **84** 74 (Jan 3) 1925

10 Zikovsky Zur Kenntnis der Agranulocytose, Wien med Wchnschr **77** 589, 1927, Zur Frage der Agranulocytose, Wien klin Wchnschr **40** 1376 and 1420, 1927

11 Turk, quoted by Weiss (footnote 6)

12 Ehrmann and Preuss Ueber Leukopenie und Schwund der Granulocyten bei Sepsis (Agranulocytose), Klin Wchnschr **4** 267, 1925

13 Lovett, R W Agranulocytic Angina, J A M A **83** 1498 (Nov 8) 1924

14 Cannon Some Unusual Dermatoses, Agranulocytic Angina, South M J **20** 141, 1927

15 Reye and Wohlwill, quoted by Leuchtenberger Ueber Agranulocytose, Klin Wchnschr **5** 1492, 1926

teristic pathologic alterations such as leukemic infiltrations in the liver, spleen, lymph nodes and kidney

(d) Aleukia (Ehrlich) is also characterized by a general hemorrhagic diathesis, thrombopenia, secondary anemia and lengthened bleeding time, such as occurs in some of the diseases already mentioned. It resembles agranulocytosis in that atrophy of the total myeloid tissue occurs but with inclusion of megakaryocytes. Moreover, myeloblasts are still present in the atrophic bone marrow.

2 Diseases showing an agranulocytic symptom complex but without gangrenous ulcers in the mouth

To this group belong various diseases such as the abdominal type of Hodgkin's disease (Jaffé,¹⁶ Feer⁵), pernicious anemia, carcinosis of the bone, miliary tuberculosis, poisonings with arsenic compounds (arsphenamine) and benzene and diseases in which roentgen-ray irradiation (especially in the treatment for chronic lymphatic and myeloid leukemia) and thorium X are employed.

3 Diseases showing similar necrosing processes in the mouth, but without an agranulocytic symptom complex

(a) Diphtheria, especially its fulminant type, in its general and local symptoms sometimes closely resembles agranulocytosis, but it is different in hematologic, bacteriologic and pathologic respects. In seven of the cases reviewed, it was specially stated that the preliminary diagnosis was diphtheria.

(b) Vincent's angina may also show local alterations similar to those found in agranulocytosis, but here also the differential diagnosis rests on the general condition of the patient, the condition of the blood, the good prognosis and the pathologic alterations.

(c) Monocytic angina (Schultz¹), like Vincent's angina, usually occurs at an earlier age (from 12 to 27) than agranulocytic angina. In this disease necrosis is restricted to the tonsils, and a generalized enlargement of the lymph nodes and of the liver and spleen occurs. The latter remains persistent for several months after recovery. The blood shows an increased number of white cells, with an absolute increase of the monocytes (from 6 to 78 per cent). Jaundice is never present, nor are hemorrhages observed. Females are not affected more than males, and the prognosis is in general good. Few fatalities are reported. The disease is apparently contagious and has a protracted course.

4 Other diseases which represent differential diagnostic possibilities

In the beginning, agranulocytosis may sometimes resemble acute cholecystitis in its abdominal manifestations. But besides the state of

16 Jaffé. Agranulocytaer Symptomkomplex bei Hodgkinschem Lymphogranulom, München med Wchnschr 73:2012, 1926

the throat and the blood, the discrepancy between the unfavorable general condition of the patient and the relatively light local symptoms in agranulocytosis will point to the correct diagnosis

COMMENT

1 Essential agranulocytosis (Schultz) can be differentiated by its clinical and pathologic symptoms from diseases showing a secondary agranulocytic symptom complex

2 The demonstration of bacteria in the blood of patients with agranulocytosis is not proof of the infectious character of the disease, because bacteria are also frequently found in later stages of leukemias and their presence is due to invasion of the body through the areas of necrosis

3 Agranulocytosis is apparently not contagious

4 Its prognosis is bad, but not absolutely infaust

5 The disease may be confused with fulminant diphtheria if an examination of the blood is not made

6 The unknown noxa injures not only the granulocytic system but the lymphatic system, as is evident from the marked absolute decrease of these cells in the blood and in the lymphatic organs. The reticulo-endothelial system apparently undergoes a compensatory hyperplasia

INGESTED CREATINE

ITS UTILIZATION AND RATE OF EXCRETION BY ARTHRITIC AND
NORMAL SUBJECTS [†]

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When creatine is administered orally to men and animals, a portion of it may be excreted in the urine apparently unchanged, the remainder being retained by the organism. If the quantity of creatine ingested is small, as was the case in some of Folin's early experiments ¹ and in a recent experiment of Rose, Ellis and Helming,² none will appear in the urine. With larger doses an appreciable quantity is excreted, but some is always retained, normally. The efficiency of the body in utilizing a given dose of creatine decreases if the administration of creatine is continued from day to day. This was clearly shown in the experiments of Benedict and Osterberg on dogs ³ and in those of Chanutin ⁴ and Rose, Ellis and Helming ² on men, in which creatinuria appeared and became more decided as the creatine feeding was persisted in. Chanutin ⁴ has pointed out that in respect to their utilization, there is a similarity between creatine and dextrose. Both substances may be completely utilized when fed in small amounts, but the capacity of the body to retain either may be readily overcome if, instead of feeding a small quantity, a massive dose is employed.

The response of the body to a single massive dose of dextrose has been extensively studied, and dextrose feeding has been used as a test to detect defective sugar metabolism. In a similar manner it may be possible to detect an abnormal creatine metabolism by observing the ability of the body to utilize a large dose of creatine. In conditions of frankly deranged creatine and creatinine metabolism, the capacity to retain administered creatine is greatly diminished as was shown by

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* The work here reported is a part of a series of studies on chronic arthritis by Ralph Pemberton, M D, of Philadelphia, in collaboration with Robert B Osgood, M D, of Boston. The expenses of this investigation were defrayed by contributions from various sources, including a number of patients.

1 Folin, O. Hammarsten's Festschr, 111. Upsala, 1906

2 Rose, W C, Ellis, R H, and Helming O C. J Biol Chem **77** 171 (April) 1928

3 Benedict, S R, and Osterberg, E. J Biol Chem **56** 229 (May) 1923

4 Chanutin, A. J Biol Chem **67** 29 (Jan) 1926

Gibson and Martin,⁵ who studied a case of progressive pseudohypertrophic muscular dystrophy with a creatinuria and a low creatinine excretion. They found that creatine when given to this patient, even in small amounts (0.5 Gm.), was promptly and completely eliminated, chiefly as creatine.

The following experiments were undertaken to compare the utilization of creatine administered as a single large dose to patients with proliferative arthritis, on the one hand, with the utilization of the same quantity by normal healthy subjects, on the other. A difference in the two groups in their ability to utilize creatine when so given would be suggestive. Pemberton and Buckman⁶ found slightly high values for creatine in the blood in half of a series of fifty cases of arthritis studied by them in the army. The frequency of the occurrence of myositis with chronic arthritis made it also seem not unlikely that the arthritic patient might exhibit a peculiar response to ingested creatine. Levene and Kristeller⁷ found a low rate of creatine catabolism in pathologic conditions involving the muscular system.

In the present experiments, the rate of excretion of the unutilized creatine has also been studied. Examination of the literature shows that studies have not been reported heretofore in which the urine has been analyzed at frequent intervals after creatine feeding to determine how rapidly the body excretes that part of the creatine which is not retained.

EXPERIMENTAL PROCEDURE

Seven women patients with active proliferative arthritis and seven persons in apparent good health, four women and three men, served as subjects for these feeding trials. Five of the women in the arthritic group were middle aged and two were young. With the exception of one elderly woman, the normal subjects were all young—interns, laboratory and hospital workers.

Each experiment consisted of a three day period, during which the following procedure was carried out. A preliminary twenty-four hour collection of urine was made during the first day. On the morning of the second day, 10 Gm. of creatine, dissolved in a glass of hot, sweetened lemonade, was given orally. The taste of the creatine was almost undetectable in the presence of the lemon juice, and nausea or gastric symptoms were not encountered.

The creatine employed was a high grade commercial product,⁸ which was found on analysis to be free from creatinine and to have a melting point, nitrogen content and water of crystallization close to that calculated for creatine.

5 Gibson, R. B., and Martin, F. T. *J. Biol. Chem.* **49**: 319 (Dec.) 1921.

6 Pemberton, R., and Buckman, T. E. *Studies on Arthritis in Army Based on 400 Cases. Studies in Relation of Creatine Metabolism to Arthritis*, *Arch. Int. Med.* **25**: 335 (April) 1920.

7 Levene, P. A., and Kristeller, L. *Am. J. Physiol.* **24**: 45, 1909.

8 We are indebted to Mr. C. Broxton Valentine, chemist of Valentine's Meat Juice Company of Richmond, Va., for this product.

During the twenty-four hours following the ingestion of creatine, collections of urine were divided into two three hour periods, one six hour period and one twelve hour period. A twenty-four hour collection of urine was made on the third day of the experiment.

During these three days, meats, gravies and soups prepared from meat stock were excluded from the diet. Other dietary restrictions were not imposed.

The following methods were used in the analysis of the specimens of urine, all of which were preserved with toluene. Folin's colorimetric method was used for the determination of creatinine,⁹ employing as standard a solution of creatinine in tenth normal hydrochloric acid. Urinary creatine was converted into creatinine by heating in the autoclave with normal hydrochloric acid as directed by Benedict and Myers.¹⁰ The total nitrogen was determined by Folin's method.⁹

TABLE 1—*The Utilization of 10 Gm of Creatine by Normal and Arthritic Subjects*

No	Condition	Sex	Creatinine Coefficient	Creatine * Excreted 24 Hours Before Feeding Gm	Extra * Creatine Excreted After Feeding Gm	Creatine * Retained Gm	Creatine Retained Per Cent
7	Arthritis	F	10.7	0	4.81	2.77	37
5	Arthritis	F	10.9	0	2.91	4.67	62
10	Arthritis	F	12.5	0.09	3.61	3.97	52
4	Arthritis	F	14.6	0.19	5.90	1.68	22
9	Arthritis	F	14.7	0.19	4.95	2.43	32
3	Arthritis	F	15.1	0.02	5.42	2.16	29
6	Arthritis	F	15.7	0.05	4.33	3.25	43
8	Normal	F	13.9	0.01	3.52	4.06	54
11	Normal	F	17.0	0.04	3.65	3.93	52
12	Normal	F	20.4	0	4.61	2.97	39
2	Normal	M	23.8	0	2.45	5.13	68
1	Normal	M	24.1	0.03	3.35	4.23	56
13	Normal	F	25.2	0	4.47	3.11	41
14	Normal	M	26.5	0	3.43	4.15	55

* Creatine values expressed as creatinine in grams, 10 Gm creatine \approx 7.58 Gm creatinine

THE UTILIZATION OF INGESTED CREATINE

The data showing the utilization of creatine by the arthritic and normal subjects, as revealed by urinalysis, are given in table 1. The results are arranged for both groups in order of increasing creatinine coefficients. It will be seen that wide individual variations in ability to retain ingested creatine were encountered, the percentage of the utilization of creatine ranging in the arthritic patients from 22 to 62 and in the normal subjects from 39 to 68. The arthritic patients were, as a whole, slightly less efficient in their ability to retain creatine. The subjects in this group, however, had lower creatinine coefficients than the normal persons, and for this reason might not be expected

⁹ Folin, O. Laboratory Manual of Biological Chemistry, ed 3, New York, D Appleton & Company, 1922.

¹⁰ Benedict, F. G., and Myers, V. C. Am J Physiol 18:397, 1907.

to have so great a capacity for retaining creatine as the normal subjects with a high creatinine coefficient and hence, perhaps, a larger storage reservoir for creatine. When the ratio of creatine retained to creatinine coefficient is considered, there do not appear to be differences between the two groups in their respective abilities to retain ingested creatine. It should be pointed out, however, that a clear relationship was not observed between the creatinine coefficient and the utilization of creatine. The largest retentions of creatine were not always associated with high coefficients, nor did those subjects with the lowest creatinine coefficients retain the smallest amount of the creatine.

As will be mentioned later, small amounts of unutilized creatine were being excreted by the arthritic patients, in contrast to the normal

TABLE 2—*Excretion of Creatinine, Nitrogen and Water Following the Ingestion of 10 Gm of Creatine*

No	Creatinine (Gm)				Total Nitrogen (Gm)			Volumes (Cc)		
	1st Day	2nd Day	3rd Day	Increase on 2nd Day	1st Day	2nd Day	3rd Day	1st Day	2nd Day	3rd Day
5	0.60	0.69	0.61	0.09	4.10	4.73	4.25	1930	1605	2410
3	0.65	0.75	0.54	0.10	5.26	5.98	5.93	1790	1455	1220
10	0.66	0.76	0.66	0.10	6.59	6.92	6.05	1665	1425	1190
4	0.73	0.67	0.76	-0.06	7.41	6.92	6.78	1575	1435	1315
6	0.76	1.06	0.87	0.30	6.72	8.09	6.08	1615	1945	2050
9	0.79	0.88	0.77	0.09	4.83	6.71	4.83	2720	2198	2595
7	0.80	0.95	0.83	0.15	7.80	8.20	5.90	3295	3365	1350
8	0.92	1.02	0.95	0.10	6.54	6.99	6.44	1030	1080	1100
11	1.03	1.23	1.01	0.23	7.54	11.25	8.97	1425	2083	1572
12	1.03	1.31	1.23	0.25	6.39	7.10	5.21	1305	1745	1605
13	1.59	1.48	1.37	-0.11	10.28	11.13	8.47	1020	1383	1524
2	1.72	2.01	1.70	0.29	10.77	10.80	10.10	1105	1095	790
14	2.13	2.17		0.04	11.04	14.11		640	1525	

subjects, during the second twenty-four hours following creatine feeding. If this had continued longer, the calculated values for utilization of creatine in table 1 would be a little high.

The data for the excretion of water, creatinine and nitrogen during this experimental regimen are recorded in table 2.

During the day of creatine feeding there was a distinct increase in the excretion of creatinine in all but two of the experiments. This increase was present only on the day when creatine was taken, and on the following day urinary creatinine had usually returned to the excretion level of the fore period.

The figures on the excretion of nitrogen are of limited value only, in view of the fact that the intake of nitrogen was not necessarily a fixed quantity during the three days of the experiment. After deducting the nitrogen contained in the urinary creatine, less nitrogen was excreted

in most of the experiments on the day that creatine was administered than on the other two days

The twenty-four hour volumes did not usually show any great variation during the course of the experiment

THE RATE OF EXCRETION OF UNUTILIZED CREATINE

The creatine content of the urine during the periods following creatine feeding is given in table 3. It was found that the fraction of ingested creatine which the body did not utilize was promptly excreted and that in most cases by the end of six hours most of the unretained creatine had appeared in the urine.

With one exception, the peak of excretion of creatine by the normal subjects occurred during the first three hours after the creatine was ingested. From this peak, excretion of creatine diminished rapidly

TABLE 3—*The Rate of Excretion of Creatine Following the Administration of 10 Gm of Creatine**

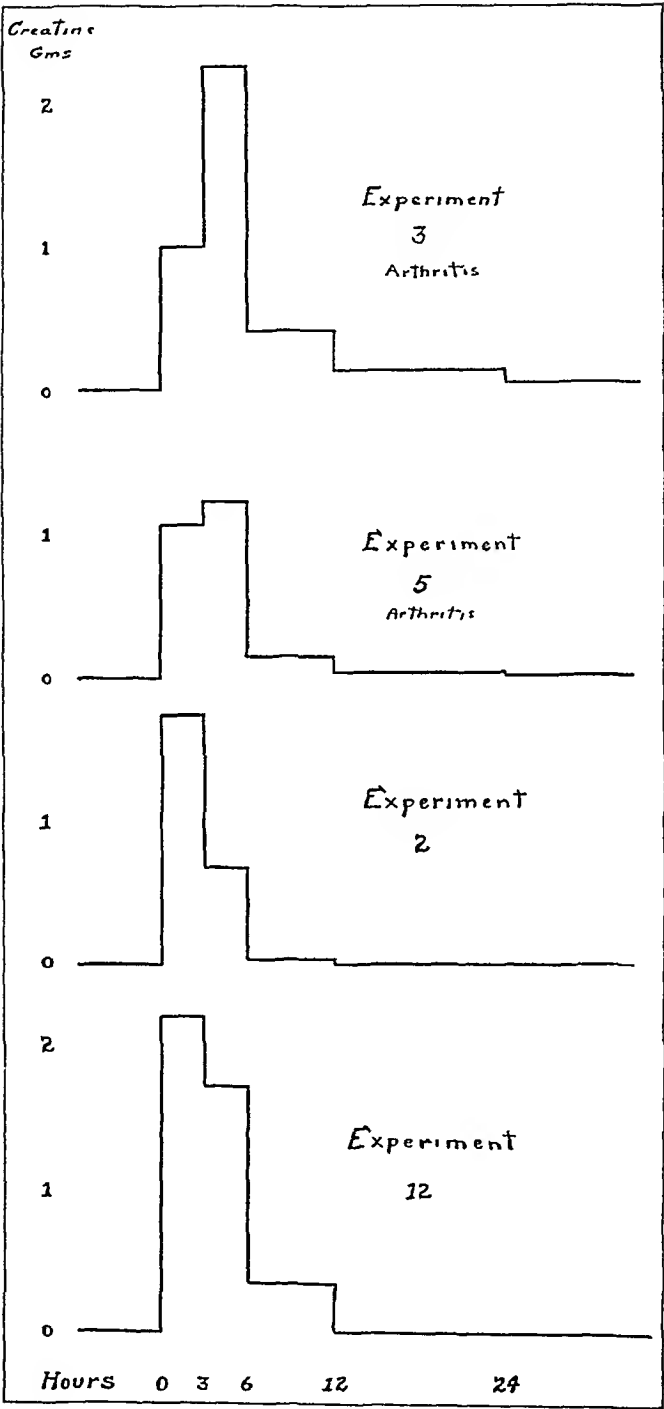
Number	Normal Subjects						Arthritic Patients							
	2	8	11	12	13	14	3	4	5	6	7	9	10	
24 hr fore period	0	0.01	0.04	0	0	0	0.02	0.19	0	0.05	0	0.19	0.07	
0-3 hrs	1.73	1.92	0.93	2.21	2.76	2.78	1.01	1.26	1.09	1.57	1.04	2.04	0.96	
3-6 hrs	0.68	1.11	1.42	1.72	1.04	0.65	2.29	1.92	1.24	1.74	2.33	1.22	1.17	
6-12 hrs	0.04	0.50	0.51	0.68	0.49	0	0.85	1.78	0.33	0.60	0.84	0.76		
12-24 hrs	0	0	0.37	0	0.18	0	0.63	0.60	0.11	0.31	0.35	0.53		
24-48 hrs	0	0	0.50	0	0	0	0.63	0.72	0.14	0.21	0.19	0.48	0.52	

* Creatine values expressed as creatinine in grams. Ten Gm creatine \approx 7.58 Gm creatinine.

and usually was completed by the end of twelve hours. In the arthritic group a definite lag in the excretion of creatine has been found. In this group, the peak of excretion was usually not reached until the second period, that is, during the third to sixth hour after the administration of creatine. The creatinuria lasted longer in these subjects than in the controls, and in all seven of the experiments on arthritis, extra creatine was being excreted during the second twenty-four hours. A similar delay in disposal of the ingested creatine was encountered only once among the supposedly healthy subjects.

In the accompanying chart the rate of the excretion of creatine, per three hours, for four subjects, two normal persons and two arthritic patients, has been plotted.

The delay in excretion of creatine and the persistence of the induced creatinuria found among the arthritic patients can hardly be attributed to a failure on the part of these subjects to store creatine, when the total utilization data are considered. Evidence has not been found in these experiments to indicate that the patients in this group are less



The three hourly rate of excretion of creatine following the administration of 10 Gm of creatine

capable than the subjects in the normal group in their ability to retain creatine when it is fed to them in a large dose

Consideration must be given to the possibility of an impaired renal function in those persons who showed a delay in the excretion of creatine. Pemberton and Foster¹¹ found normal values for urea and nonprotein nitrogen in the fasting blood in patients with arthritis. They detected in their subjects a slight delay in the excretion of water, nitrogen and salt, following the Mosenthal test meal, but were unable to conclude that any marked dislocation of renal function is present in chronic arthritis. If the delayed excretion of creatine is to be ascribed to renal insufficiency, which seems doubtful, there is then available in creatine feeding a delicate test for the function of the kidney.

The observation that in all the arthritic subjects and in one of the normal subjects a delay in the excretion of creatine follows massive administration of creatine can only be stated as fact at this time without attempting to give an explanation of it. It is, however, of considerable interest to recall that the arthritic patient frequently exhibits a delay in disposal of sugar following ingestion of dextrose, despite the fact that there is no evidence of failure of combustion of dextrose by him. This delayed "sugar removal" has been definitely referred in the arthritic patient to a defective blood supply to those parts actively concerned in the removal of sugar from the blood.¹² The somewhat similar delay in disposal of creatine, when fed in large amounts, may result from some factor similar to that causing the delay in the disposal of sugar.

SUMMARY

The utilization of creatine, when administered orally in a single 10 Gm dose, has been studied.

The rate of excretion of creatine and the persistence of the creatinuria induced by the ingestion of this amount of creatine have also been determined.

Individual variations of considerable magnitude were found in the amounts of the ingested creatine utilized. When the differences in creatinine coefficients are considered, the patients in the arthritic group proved to be as efficient as the subjects in the normal group in their ability to retain creatine.

11 Pemberton, R, and Foster, G L. Studies on Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, *Arch Int Med* **25** 243 (March) 1920.

12 Pemberton, R, Cajori, F A, and Crouter, C Y. Influence of Focal Infection and Pathology of Arthritis, *J A M A* **85** 1793 (Dec 5) 1925.

The rate of excretion of the excess creatine was slower, however, in the arthritic patients than in the normal subjects. The peak of excretion was not reached as soon after the creatine was administered, and the creatinuria persisted longer in the arthritic patients than was the case in all but one of the normal control subjects.

The fact that a delay has been encountered in arthritis in the disposal of ingested dextrose suggests that the factors responsible for the slow rate of excretion of creatine may be similar to those which cause the delay in the removal of ingested dextrose. In the case of dextrose, the delay in the removal of sugar has been referred to a disturbance of peripheral blood flow in patients with arthritis.

THE EFFECTS OF SERUMS FROM NORMAL AND FROM ANEMIC PERSONS ON THE GROWTH OF SEEDLINGS [†]

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The impetus given to the study of pernicious anemia by the discovery of Minot and Murphy ¹ that a remission could be induced and maintained by a diet rich in liver or an effective liver extract has reopened several problems in connection with the disease. The presence of toxic substances in the blood stream as an etiologic factor has been considered by Macht ² although, as Minot pointed out,¹ these substances could be a result of the altered metabolism produced by the disease rather than a causative factor. In a series of studies on the effect of serums taken from patients with pernicious anemia and other serums on the growth of lupine seedlings, Macht ³ found that the average coefficient of growth in Shive's solution which contained normal blood serum was 75 per cent of the growth of the seedlings as compared with similar growth in Shive's solution alone. On the other hand, the indexes of growth obtained with specimens of blood from patients with pernicious anemia varied from 28 to 51 per cent, giving an average coefficient of 44 per cent. This procedure was suggested as a method of differential diagnosis, when a coefficient of growth was obtained of 50 per cent or less, as compared with a normal index of from 50 to 75 per cent, the results were in favor of pernicious anemia. The hydrogen ion concentration of the serums did not play a rôle in explaining a selective toxicity of the toxin for plants. The serums of patients with secondary anemia were practically nontoxic. It was possible to detoxify the serum of patients with pernicious anemia by exposure of the serum in a quartz tube to

[†] From the Simpson Memorial Institute for Medical Research, Ann Arbor, and the Department of Plant Physiology of the University of Michigan

1 Minot, G R, and Murphy, W P. A Diet Rich in Liver in the Treatment of Pernicious Anemia, J A M A **89** 759 (Sept 3) 1927

2 Macht, D I. Etiology, Diagnosis and Treatment of Pernicious Anemia, J A M A **89** 753 (Sept 3) 1927

3 Macht, D I, and Lubin, D S. A Phyto-Pharmacological Study of Menstrual Toxin, J Pharmacol & Exper Therap **22** 413 (Jan) 1924. Looney, J M, and Macht, D I. The Relation Between the Undetermined Nitrogen of the Blood and Its Toxicity to *Lupinus albus* Seedlings, J Biol Chem **63** 60 (Feb) 1925

ultraviolet light This phenomenon was enhanced by the addition of sensitizers as tetrabromfluorescein or similar substances After a transfusion of blood from a patient with pernicious anemia, the phytotoxic index approached the normal A similar effect was noted after the patient had been treated with a diet rich in liver, although the effect was much less marked, and the detoxification was not complete A decrease in the toxicity of the blood was noted after patients with pernicious anemia were irradiated with ultraviolet light, with the possibility of a slightly more definite action after the treatment of the patients with eosin as a sensitizer Treatment with organic mercurials also caused a detoxification of the blood serums Macht's work points to the presence of a definite substance in the blood serums of patients with pernicious anemia, which he believes to be related etiologically to the disease and which is phytotoxic

To determine the value of this test in the differential diagnosis, as well as to note any changes which feeding of liver would bring about, the blood of twenty-five normal persons as well as thirty specimens of blood of fifteen patients with pernicious anemia in various stages of the disease was studied, together with some specimens from seven patients with other types of anemia (Sixty-two serums were tested, using 1,260 seedlings)

METHOD OF STUDY

The blood serums were examined, and the technic outlined by Macht³ was used Briefly, the procedure was as follows *Lupinus albus* seeds of approximately the same size were soaked in a jar of clean tap water overnight On the following morning these seeds were taken from the jar of tap water and placed with the hilum down in a pot of moistened, clean moss of the genus *Sphagnum* After covering these seeds with this moss, they were placed in the dark at a temperature of 68 F, and were left from two and a half to three days, according to the growth exhibited On reaching the proper length the seedlings were set up in the following manner Hard glass test tubes (1 5 by 20 and a content of 30 cc) were used, these were placed in holes in a wooden block holding fifteen test tubes in an upright position Shive's solution R5C2 (10 4 cc of 0 5 molar solution of calcium nitrate, 30 cc of 0 5 molar solution of magnesium sulphate, 36 cc of 0 5 molar solution of monopotassium acid phosphate, 1 liter of distilled water) was made of Baker's chemically pure analyzed chemicals⁴

Blood was obtained from patients and from members of the staff of the Simpson Memorial Institute one hour before it was used The blood was collected in sterile test tubes from patients before they had eaten breakfast, neither antiseptics nor anticoagulents were added After the serum had separated from the clot, the material was centrifugalized and transferred with sterile pipets to sterile test tubes A 1 per cent solution from each serum was made in Shive's solution For each observation, a set of fifteen seedlings was used for each solution The 1 per cent solution was mixed and shaken well in flasks and then poured into the test tubes to within from 1 to 1 5 cm from the top (27 cc of solution) For each

4 Shive, W J A Study of Physiological Balance in Nutrient Media, *Physiological Research* 1 327 (Nov) 1915

experiment, serum from a normal person was used as a control, as well as seedlings in Shives solution alone. When these solutions were prepared, seedlings of *Lupinus albus* of approximately the same length were selected. These seedlings were carefully measured, from the darkened region of demarcation of the root and stem to the tip of the root, on a centimeter ruler fastened to a piece of soft wood. This measurement was recorded, and the seedlings were placed in the proper test tube. The seedling was held in position by hanging it over the edge of the test tube by the cotyledons and supporting it by pledgets of cotton. The p_H values were determined for the solutions colorimetrically. Shives solution averaged p_H 4, and the 1 per cent serum solution averaged p_H 4.4, there was some little variation.

The tubes containing the seedlings were then placed in the dark at a temperature of 68°F. At the end of twenty-four hours, measurement of the roots was again made and recorded. Similar measurements were recorded at the end of another twenty-four hours (forty-eight hours). At the end of forty-eight hours the p_H values were determined. There was little variation for the p_H values for the different solutions (Shive's p_H 4, 1 per cent solution p_H from 4.3 to 4.4).

Since the increase in growth was important, this observation was made for each seedling at twenty-four and forty-eight hour periods. These figures for a given set of observations were added together and the average found (in centimeters) for the seedlings in a given solution. For each solution the increase in centimeters of the length of the root for twenty-four and forty-eight hours was compared to the increase in growth in Shive's solution and that in the serum of normal persons. The percentage growth in each solution was also calculated. The growth in centimeters in Shive's solution was taken as 100 per cent and that in the serum solutions calculated as a percentage of this. This procedure was done separately for each set of observations.

RESULTS

The accompanying tables give the serums employed, the growths of the seedlings in centimeters and the percentage growth for twenty-four and forty-eight hour periods in different solutions used.

COMMENT

From the foregoing observations an average of growth for twenty-four hours was established for seedlings in a normal blood serum. To establish this average, fifteen seedlings were grown in each of the twenty-five normal serums, making a total of 375 seedlings. The average coefficient of growth for the seedlings in normal serums was 76.5 per cent as compared to that in Shive's solution. Several of these twenty-five normal serums were taken from men before they had eaten breakfast in order to determine whether or not the coefficient of growth would be altered by processes of digestion. Comparisons failed to show a significant difference.

It is to be noted, however, in establishing this average for growth in normal serum, that there was a wide range of variations in individual sets of serums (from 50 to 97 per cent).

In the thirty specimens of serum taken from fifteen patients with pernicious anemia, the indexes of growth obtained varied from 59 to 94.3 per cent, with an average of 76.6 per cent. This average was obtained from patients with pernicious anemia per se without regard to treatment with liver or to clinical conditions. If, from this group, those patients (five in all) who had not had treatment with liver at the time the serum was obtained were separated, the indexes of growth varied from 60.1 to 86.9 per cent with an average of 75.4 per cent.

TABLE 1—*Serums, Growth of Seedlings and Percentage Growth in Twenty-Four and Forty-Eight Hour Periods*

Case No.	Sex	Day of Observation	Red Blood Cells Millions per Cubic Millimeter	Per Cent Hemoglobin	Bilirubin Mg per Hundred Cubic Centimeters	Liver or Liver Extract	Clinical Condition	24 Hours Growth of Roots in Percentage of Growth in Shive's Solution
1	M	1	3.5	53	0.8	+	Mod sick	67.4
		5	4.7	83		+	Good	93.8
		11	5.21	65	1.1	+	Good	73.3
2	M	1	1.8	35	2.3	0	Very sick	81.0
		17	3.3	53	0.9	+	Good	85.6
		31	4.23	64	0.9	+	Good	93.4
3	F	1	2.3	50	0.7	+	Very sick	71.2
		8	3.1	49	0.4	+	Improved	65.3
		15	4.0	63	0.3	+	Good	84.5
4	M	1	1.04	26	1.2	0	Very sick	60.1
		23	2.1	44	1.1	+	Good	75.3
		31	2.9	56	0.5	+	Good	59.7
5	M	1	0.78	18	1.6	(+)	Sick	77.3
		36	3.2	50	0.5	+	Improved	63.7
6	M	1	2.6	55	1.0	0	Sick	86.9
		6	2.4	53	0.5	(+)	Improved	75.0
		28	4.19	72	0.3	+	Good	82.7
7	M	1	0.99	23	1.3	(+)	Sick	80.7
		14	1.5	27	0.8	+	Good	69.5
8	F	1	2.07	40	2.4	0	Sick	79.5
		22	4.2	60	0.5	+	Good	83.6
9	M	1	4.0	80	0.4	+	Good	80.1
		9	4.0	80	0.5	+	Good	77.0
		28	4.34	84	0.3	+	Good	80.1
10	M	1	1.14	22	2.3	(+)	Sick	80.2
11	F	1	4.7	80	0.4	+	Good	64.3
12	M	1	1.2	29	3.8	0	Sick	69.4
13	M	1	2.3	60	0.2	+	Sick	85.4
14	F	1	3.87	55	0.3	+	Good	74.3
15	M	1	2.85	70	0.7	+	Sick	76.2
Average								76.6

+ Indicates effective liver extract or liver therapy, 0, indicates no liver or extract given, (+) indicates experimental liver extract which did not contain the effective principle for stimulation of the blood.

The remaining patients who had been treated with liver or liver extract showed a variation of from 59.7 to 93.8 per cent with an average of 76.8 per cent of growth of the root. Care was taken to secure serum from patients of the male sex and from females who were not menstruating.

The coefficient of growth for forty-eight hours was determined, and essentially the same percentages were obtained as those for twenty-four hour periods. Marked toxicity for serum from patients with pernicious anemia was not noted.

As in a given set of seedlings grown from identical seeds under identical conditions, a decided variation in the growth of the root was noted, it was considered advisable to select seedlings which were of approximately the same length for comparative observations. When direct comparisons are made between seedlings of exactly the same original length after a twenty-four hour period, a consistent variation does not seem to exist between those grown in normal serum and those grown in serum from patients with pernicious anemia. In fact, the variation in extremes of growth in blood serum of any type studied does not show any more variation than individual seedlings grown in Shive's solution.

When results obtained so far are considered, one finds that normal blood serum is toxic to seedlings as compared to Shive's solution, but there does not seem to be any evidence that serums of patients with pernicious anemia are any more toxic than is normal blood serum itself. Moreover, there is not any appreciable difference between the coefficients of growth in serums from patients who were not treated and those from patients treated with liver or liver extract.

A further analysis of the records and a comparison of the degree of illness with growth of the roots in centimeter at first glance seems to show a correlation. When the percentage increase in growth in Shive's solutions is calculated, however, only in case 2 is there correlation.

There does not seem to be any relation between the coefficient of growth and clinical condition as measured by the red blood cell count, the hemoglobin percentage and the amount of bilirubin in the blood. We felt that the toxicity of normal blood might be caused by a difference in the hydrogen ion concentration, p_H of a 1 per cent blood solution differs from the p_H of Shive's by 0.4+. When the hydrogen ion value of Shive's solution was changed to correspond to that of the 1 per cent serum solution, by the addition of sodium hydroxide, the growth was equal to and in a few cases greater than that in the normal Shive's solution. It is evident that the slightly higher hydrogen ion value of the serum solutions would tend to enhance the growth, if any difference in growth was evident.

The fact that a 1 per cent serum solution supports more bacterial growth than Shive's solution probably does not explain the difference in growth in the latter solution and in a 1 per cent serum solution, for the bacterial growths at the end of twenty-four hours were slight as indicated by cultures and plates.

The seedlings tested with the serums from patients with secondary anemia (leukemia, infection with *Dibothryocephalus latus*, carcinoma, duodenal ulcer) did not show any marked difference in the rate of

growth from those tested with serum from normal persons or from patients with pernicious anemia (table 2) Their coefficients of growth varied from 60.6 to 88 per cent with an average of 74.7 per cent

With such slight differences as those found in serums from normal persons and from persons with pernicious anemia, it is impossible for a diagnosis to be based on the percentage increase in growth of seedlings of *Lupinus albus*

When one surveys this experiment from the standpoint of the practical application of phytopharmacology as a new branch of science,

TABLE 2—*Serums, Growth of Seedling and Percentage Growth for Twenty-Four and Forty-Eight Hour Periods*

Test Number	Normal with Break-fast	Normal without Break-fast	Anemia, Not Pernicious Anemia	Pernicious Anemia		
				Good Condition	Moderately Sick	Very Sick
1	69.1					Case 3, 71.2
2			80.3	Case 9, 80.1		
3	87.3				Case 3, 65.3	Case 1, 67.4
4	97.4			Case 1, 93.8 Case 3, 84.5 Case 9, 77.0		Case 2, 81.0
5						
6	50.0		60.6 88.0			
7	82.3 82.7	76.9				Case 6, 86.9 Case 13, 85.4
8	86.9	85.6		Case 2, 85.6		
9	81.4			Case 9, 80.1	Case 6, 75.0	
10		73.5				Case 5, 77.3
11		63.4				Case 4, 60.1
12	76.2 71.3	88.1		Case 2, 93.4		
13	68.4	74.9	75.2			
14	83.7			Case 1, 73.3 Case 14, 74.3		
15	80.3					Case 8, 79.5 Case 15, 76.2 Case 7, 80.7
16	88.7			Case 6, 82.7		
17	61.8		72.6	Case 4, 75.3		
18	72.4		78.3			Case 10, 80.2
19	63.3			Case 4, 59.7 Case 7, 69.5 Case 11, 64.3 Case 8, 83.6	Case 5, 66.7	
20	74.4					
21	72.9					
22			68.0			Case 12, 69.4
Average	75.2	77	74.7	78.5	69	76.3

several notable points present themselves. Plant growth like animal growth is governed not only by environmental but also by hereditary influences. Thus, one sees that in the foregoing experiments in which environmental factors such as food, temperature, water and humidity are constant, there are marked variations in the growth of the roots of seedlings which must be explained by hereditary factors. It is impossible to estimate these inherited factors of growth from external examination. Even if we select seedlings having cotyledons of the same size and with an equal supply of reserve food, it is conceivable that certain cotyledons contain quantitative chemical differences which may have an important bearing on early growth of the root.

We now control this factor of heredity by using a large number of seedlings and attaching significance to the average. As the science of phytopharmacology progresses, it may be found advisable to secure seeds from a given plant and an inbred strain for comparative observations. Such controls over inherited factors are decidedly favorable in securing accurate results. It is this control that man has over inherited factors in plants, which he does not possess in animals, and the small cost of experiments carried on with plants that makes plants so important to future workers.

SUMMARY AND CONCLUSIONS

1 Seedlings of *Lupinus albus* grown in Shive's nutrient saline solution and containing serum from normal persons showed an average rate of growth of 76 per cent of the rate of growth in Shive's solution alone. The rate of growth was slightly, but not significantly, higher in the serum of persons in the postdigestive state, as compared with those who had taken food a short time before.

2 The growth of seedlings in solutions containing serum from patients with pernicious anemia did not vary significantly from that in serum taken from normal persons.

3 An appreciable difference was not noted between the coefficient of growth for lupine seedlings in serum from patients who were not treated, that in the serum from patients with pernicious anemia who were treated with liver was noted.

4 A relation was not found between the coefficient of growth and the clinical condition of the patients with anemia as measured by degree of illness, red blood cell count, hemoglobin or bilirubin in the blood.

5 With the seedlings used, it was not possible to diagnose pernicious anemia by the effect of blood serum on the growth of the root.

6 Whatever differences of growth may have been influenced by the serums (environmental factors) may have been overshadowed by the inherent variations of growth of the seedlings of different parentage with dissimilar tendencies of rate of growth (hereditary factor). This may account for the differences in the results of the observations from those reported by others.

7 The observation of Macht that serum from patients with secondary anemia does not depress the growth of seedlings is confirmed.

BILE ACIDS IN JAUNDICE*

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The present day evidence, although incomplete, is in favor of the view that the bile acids are formed in the hepatic parenchyma, but what is the evidence on which this assumption is based? For many years, it was assumed that bile pigments were formed in the liver and could not be formed elsewhere. It is becoming increasingly evident that bile pigments are formed largely outside the liver and eliminated through the liver. That bile pigments are formed rapidly and abundantly in the circulation outside the liver is confirmed and extended by observations made by Mann and his collaborators,¹ who employed complete extirpation of the liver and infusion of sugar in experiments lasting from twelve to eighteen hours. Is it possible that bile acids, in like fashion, may be formed outside the liver and merely eliminated by it? A discussion of these points has been made in a recent review² and in publications by Whipple and his collaborators,³ although their explanation that the bile acids are produced in the liver is far from being convincing. Further discussion will be deferred to a later section. In the clinical study of hepatic disease, much interest has centered around the possibilities of dissociated jaundice and variations in bile acid metabolism independent of changes in the bile pigments. Much of this⁴ work has been based on variations in the surface tension of the urine, as shown by Hay's test⁵ which is not specific for bile acids and does not permit

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1 Mann, F C, Magath, T B, and Bollman, J L. Studies on Physiology of Liver, Formation of Bile Pigment after Total Removal of Liver, *Am J Physiol* **69** 393 (July) 1924

2 Whipple, G H. Origin and Significance of Constituents of Bile, *Physiol Rev* **2** 440 (July) 1922

3 Foster, M A, Hooper, C W, and Whipple, G H. The Metabolism of Bile Acids. IV. Endogenous and Exogenous Factors, *J Biol Chem* **38** 393 (June) 1919. Smyth, F S, and Whipple, G H. Bile Salt Metabolism, Influence of Chloroform and Phosphour on Bile Fistula Dogs, *J Biol Chem* **59** 623 (April) 1924

4 Borchardt, H. Bile Acids in Urine, Blood, Duodenal, and Cerebrospinal Fluid in Icterus, *Klin Wchnschr* **2** 541 (March 19) 1923. Hoover, C F, and Blankenhorn, M A. Dissociated Jaundice, *Arch Int Med* **18** 289 (Sept) 1916. Beth, H. Pathology of Secretion of Bile, *Wien Arch f inn Med* **2** 563 (June) 1921. Rosenthal, F, and Falkenhause, M F. Secretion of Biliary Acids in Man, *Klin Wchnschr* **2** 1487 (Aug 6) 1923

5 Hay, Mathew, 1886. This test was outlined by Muller, H, Jr. Hay Test for Bile Acids in Urine, *Schweiz med Wchnschr* **51** 821 (Sept 8) 1921

of a quantitative study⁶ The application of van Slyke's gasometric method to the determination of bile acids in small amounts of bile from dogs by Foster and Hooper⁷ and by Schmidt and Dart⁸ has made possible the accumulation of valuable data concerning the excretion of bile acids in the bile Schmidt and Merrill⁹ have further devised a method of analyzing the bile acid in urine, but these methods are not applicable to the smaller amount of bile acids in the urine and blood

Szilárd¹⁰ recently described a comparatively simple colorimetric method for the estimation of the bile acids of blood plasma or serum With this technic, bile acids may be determined in from 4 to 5 cc of serum It has been my experience that, within the limits of experimental error, this method yields a quantitative recovery of taurocholic or glycocholic acids when their concentration lies between 10 and 100 mg per hundred cubic centimeters The best results are obtained by employing a sufficient volume of plasma or serum so that there will be about 0.5 or 2 mg of bile acids for the analysis¹¹

Brulé¹² suggested that bile acids are essential for the absorption of fats from the intestine, and it was on this basis that his "hemoconia" test was devised Normally, there is an increase in ultramicroscopic blood fat after a fat meal, this increase does not occur unless bile acids are present in the duodenum

A fact established early in the history¹³ of the function of bile was the "circulation of the bile acids" There is no evidence, however, for a circulation of the bile pigments¹⁴ The pigments, apparently, do not fulfill a useful function and are true waste products Bile acids are rapidly absorbed from the intestinal contents and reappear in the bile In the dogs in which they created bile fistulas, Foster, Hooper

6 Adler, A., Solti, J., Hermer, J., and Schmid, E. Action of Bile Acids in Organisms, *Deutsche med. Wchnschr.* **51** 1689 (Oct. 9) 1925

7 Foster, M. A., and Hooper, C. W. The Metabolism of Bile Acids. I. A Quantitative Method for Analysis of Bile Acids in Dog's Bile, *J. Biol. Chem.* **38** 355 (June) 1919

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12 Brulé, M. *Recherches sur les icterus les retentions biliaires par insuffisance hépatique*, ed. 3, Paris, Masson et Cie, 1922

13 Schiff, M. *Arch. f. d. ges. physiol.* **11** 166, 1875

14 Hooper, C. W., and Whipple, G. H. *Am. J. Physiol.* **42** 264 (Jan.) 1917

and Whipple¹⁵ noted that when moderate amounts of taurocholic acid (about 1.8 Gm) are given by mouth, about 90 per cent of the contained taurocholic acid is excreted during the first four hours, but when large doses (from 8 to 11 Gm of taurocholic acid) are administered, the cholagogue effect is prolonged for many hours or days.

In a previous paper,¹¹ 100 cases of jaundice were reported, and particular attention was paid to the significance of bile acids in the blood. The object of this communication is to report further studies of bile acids in the blood and in the urine in a series of thirty-two cases representing different types of jaundice.

Bernheim,¹⁶ Shattuck, Preston and Browne¹⁷ and Shattuck, Preston and Killian¹⁸ found the icterus index of the blood serum the most dependable gage of the hyperbilirubinemia, consequently, in this investigation the icterus index was utilized for estimation of the bilirubin of the blood serum. My¹⁹ method was employed for the bile acids in the urine, and for the urobilin, Elman and McMaster's²⁰ method was adopted.

TABLE 1—*Normal Control Cases*

	Blood				Urine			
	Icterus Index		Bile Acids, Mg per 100 Cc		Urobilin, Mg per 100 Cc		Bile Acids, Mg per 100 Cc	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
10 normal cases	4.4	7.0	5.0	12.0	0	0	0	Trace
Average		5.7		7.0		0		0

RESULTS

Normal Control Cases—In table 1 are presented ten normal control cases without suspected or proved injury to the liver. The icterus index was normal, varying from 4.4 to 7. The average figure was 5.7. Van den Bergh's bilirubinemia test was negative in all cases except one, in

15 Foster, M. G., Hooper, C. W., and Whipple, G. H. The Metabolism of Bile Acids. III. Administration of Stomach of Bile, Bile Acids, Taurine, and Cholic Acid to Show the Influence upon Bile Acid Elimination, *J. Biol. Chem.* **38**: 379 (June) 1919.

16 Bernheim, A. R. Icterus Index (A Quantitative Estimation of Bilirubinemia), Aid in Diagnosis and Prognosis, *J. A. M. A.* **82**: 291 (Jan. 26) 1924.

17 Shattuck, H., Browne, J. C., and Preston, M. Clinical Value of Some Recent Test for Liver Function, *Am. J. M. Sc.* **170**: 510 (Oct.) 1925.

18 Shattuck, H., Killian, J. A., and Preston, M. Comparison of Quantitative Methods for Bilirubin of Blood, *J. Lab. & Clin. Med.* **12**: 802 (May) 1927.

19 Katayama, I. A Colorimetric Method for the Determination of Bile Acids in Urine, *J. Lab. & Clin. Med.*, to be published.

20 Elman, R., and McMaster, P. D. Urobilin Physiology and Pathology, Quantitative Determination of Urobilin, *J. Exper. Med.* **41**: 503 (April) 1925.

which the indirect reaction was weakly positive. The bile acids of the blood serum ranged from 5 to 12 mg per hundred cubic centimeters estimated as sodium glycocholate, the average being 7 mg. Tests for the excretion of urobilin in the urine were negative in all cases. The tests for bile acids in the urine were negative, except in one case that showed a trace.

Cholecystitis and Cholelithiasis—In table 2 are grouped eight cases of cholecystitis and cholelithiasis, and in seven of these the diagnosis was verified by operation or autopsy. Four patients (patients 1, 2, 4 and 8) were clinically jaundiced, giving figures for the icterus index that were above the zone of latent jaundice. These four cases showed evidence of biliary obstruction. In the remaining instances, the icterus index varied from 7.5 to 19.4. It is significant that in all of these patients there is seen a distinct increase in the concentration of bile acids in the blood serum without any relation to the bilirubin. The concentration of bile acids was greater in some of these cases with low icterus indexes than in those with hyperbilirubinemias. The output of urobilin in the urine varied from traces to 2,613 mg for twenty-four hour periods. All of these patients excreted bile acids in the urine, ranging from 9.6 to 268.6 mg for twenty-four hours. It is of interest to note that the bile acids appear in the urine when the concentration of bile acids in the blood serum exceeds 20 mg per hundred cubic centimeters. There seems to be no relation between the output of bile acids and the excretion of urobilin in the urine.

A. A., a man, aged 49, had a history of clay colored stools for three months. On admission to the hospital, the icterus index was 78.5 and the bile acids, 30 mg per hundred cubic centimeters of blood serum. A month later, the patient had improved on medical treatment, and the icterus index fell to 21.4 and the bile acids of the blood decreased to 18.5 mg per hundred cubic centimeters. During this time, the excretion of urobilin for twenty-four hour specimens ranged from 33 to 752 mg, and the output of bile acids in the urine varied from 21.6 to 149.6 mg for twenty-four hour periods.

Disease of the Liver—In table 3, data are presented for four patients with diseases of the liver representing varying degrees of hyperbilirubinemia, the icterus index varying from 32.4 to 153. All of these patients presented abnormally high figures for bile acids ranging from 32 to 478 mg per hundred cubic centimeters of serum. Urobilin was excreted in the urine in all cases, except in case 4 (C. P.), that of a patient with carcinoma of the liver associated with complete biliary obstruction. The bile acids were present in the urine in all cases. The amounts, however, were relatively small and fairly constant.

J. S., a girl, aged 9 years, was admitted to the hospital on Sept. 8, 1927, complaining of chronic jaundice with enlargement of the liver and spleen of five months' duration. She had been treated medically without results. Exploratory

TABLE 3—*Disease of the Liver*

Case	Age	Sex	Date, 1927-28	Blood				Urine				Comment		
				Icterus Index	Van den Bergh		Bile Acids, Mg per 100 Cc	24 Hr Vol Cc	Urobilin		Bile Acids			
					Direct	Indirect			Mg per 100 Cc	Mg per Vol	Mg per 100 Cc		Mg per Vol	
1 J S	S	F	9/9	75.0	++++	++++	39.0	320	6	19	11.6	65.9	Acute toxic hepatitis (biliary cirrhosis), autopsy	
			9/11											
			9/14	78.9	++++	++++	28.6	500	9	15	13.2	66.0		
			9/15											
			9/21	60.0	++++	++++	25.0							
			9/22											
			9/26											
2 F M	53	M	9/26	76.5	++++	++++	23.2	330	0	0	7.0	20.3	Atrophic cirrhosis of the liver, myocarditis, syphilis (autopsy)	
			9/28											
			9/29											
			10/5					370	Trace	Trace	Trace	Trace		
			9/9	32.4	++	+++	32.0	370	188	696	7.0	26.0		
3 J B	56	M	1/12	122.0	++++	+++	17.8	150	94	141	12.5	188	Carcinoma of the liver (autopsy)	
			1/16	136.3	++++	++++	36.1	90	24	22	11.1	12.7		
			1/21	112.7	++++	++++	11.5							
4 C P	15	F	2/13	153.0	++++	+++	45.5	115	0	0	15.8	18.2	Carcinoma, metastasis to the liver, carcinoma of the esophagus (squamous cell type)	
			2/14					160	0	0	15.0	21.0		
			2/15					210	0	0	14.0	29.1		

laparotomy was done and a drainage tube inserted to the gallbladder (October 3), and a section of the liver was removed for microscopic study. The diagnosis was acute toxic hepatitis. Postoperative pneumonia and a marked abdominal distention developed. The patient became progressively worse after the development of pneumonia and died three days after the operation. The icterus index was 75 and the serum bile acids, 39 mg per hundred cubic centimeters on admission. The bile acids gradually decreased to 23.2 mg after twenty days, while the bilirubin in the blood remained unchanged. The output of bile acids in the urine for twenty-four hours was 65.9 mg at first. This gradually decreased to a trace after four weeks and just before death.

Catarrhal Jaundice—Table 4 presents seven cases of catarrhal jaundice in which the diagnosis was made according to the criteria of Klemperer, Killian and Heyd²¹. A hyperbilirubinemia is seen in all cases and an increase in the bile acids of the blood ranging from 31.2 to 53.5 mg per hundred cubic centimeters. However, the bile acids in cases 1, 3 and 6 did not show a decrease paralleling the drop in the icterus index, on the contrary, a slight increase was noted in case 1. Case 5 showed a gradual decrease in the bile acids of the blood paralleling the diminution of icterus index. Marked fluctuations were noted in the excretion of urobilin. In some instances (cases 2, 6 and 7), the curve showed peaks of large amounts and then dropped off to a scanty excretion or even a negative reaction within twenty-four hours, with a prompt subsequent rise. All of these patients excreted bile acids in the urine, and marked variations were noted. They ranged from 18.4 to 264.5 mg for twenty-four hours.

A. O., a boy, aged 7 years, was admitted to the hospital on Dec. 6, 1927, with a history of a sudden onset of jaundice and indigestion. The icterus index was 62.5 and the bile acids in the serum, 31.2 mg per hundred cubic centimeters, the output of bile acids in the twenty-four hour urine was 93.6 mg. The urobilin test gave a negative reaction, but the following day the urobilin reached 141 mg for twenty-four hour urine. A week later, the patient had improved on a fat-free diet, rest in bed and magnesium sulphate therapy. The icterus index decreased to 19.5, but the bile acids in the blood remained unchanged. The output of urobilin in the urine increased to 364 for twenty-four hours. The bile acids in the urine decreased to 32 mg for twenty-four hours.

Obstructive Jaundice—Five cases of obstructive jaundice have been studied and the data condensed in table 5. An increase in the icterus index was seen in all cases. The bile acids of the blood serum were above normal, but this increase does not parallel the rise in icterus index. Urobilin was absent or was excreted in minute amounts. When the obstruction is relieved, as in case 1, urobilin reappears in the urine.

21 Klemperer, P., Killian, J. A., and Heyd, C. G. Pathology of "Icterus Catarrhalis," Arch. Path. 2: 631 (Nov.) 1926. Heyd, C. G., Killian, J. A., and Klemperer, P. Pathogenesis of Jaundice, Surg. Gynec. Obst. 44: 489 (April) 1927.

TABLE 4—*Catarrhal Jaundice*

Case	Age	Sex	Date, 1927-28	Blood			Urine				Comment		
				Icterus Index	Van den Bergh		Bile Acids, Mg per 100 Cc	24 Hr Vol Cc	Urobilin			Bile Acids	
					Direct	Indirect			Mg per 100 Cc	Mg per Vol		Mg per 100 Cc	Mg per Vol
1 M N	40	F	12/ 9	151.6	++++	++++		480 900	94 188	431 1,692	8.1 11.8	10.3 106.2	Day specimen Night specimen
			12/12	154.5	++++	++++	32.1						Acute catarrhal jaundice
			12/16	138.8	++++	++++	32.0						
			12/22	115.4	++++	++++	41.0						
			12/27					1,710	188	3,271	15.2	264.5	
2 E H	6	F	12/21	29.1	+	++	33.3	340 260	188 0	639 0	15.0 11.0	51.0 28.6	Acute catarrhal jaundice
			12/27										
3 W F	43	F	1/ 5	136.3	++++	++++	15.1	460	188	865	11.5	66.7	Acute catarrhal jaundice with cholecystitis
			1/12	120.0	++++	++++	53.5	160	282	1,297	4.0	18.4	
			1/18	18.1	++++	++++	41.6						
4 L R	38	M	10/17	83.3	++++	++++	36.0		732 376		12.0 15.0		Acute catarrhal jaundice
			10/19										
5 P L	55	M	10/18	60.0	++++	++++	42.0	1,060	470	1,982	12.0	127.2	Catarrhal jaundice
			10/21	15.5	++++	++++	21.0						
			10/28	32.6	++++	++++	15.5						
6 G O	7	M	12/ 7	62.5	++++	++++	31.2	620	0	0	15.1	93.6	Acute catarrhal jaundice Duodenitis
			12/ 8					150	94	141	16.5	20.3	
			12/10					260	140	364	12.3	32.0	
			12/11	19.5	±	+	31.2						
7 R E	34	M	2/21	19.2	+++	+++	53.5	1,130	94	1,062	17.3	105.5	Catarrhal jaundice
			2/26					580	Trace	Trace	15.0	87.0	
			2/27										
			2/28	41.4	+++	+++							

TABLE 5—*Obstructive Jaundice*

Case	Age	Sex	Date, 1927-28	Blood			Icterus Index	Urine			Comment	
				Van den Bergh		Bile Acids, Mg per 100 Cc		Urobilin		Bile Acids		
				Direct	Indirect			Mg per 100 Cc	Mg per Vol			Mg per 100 Cc
1 J S	58	M	10/10	++++	++++	24.0	1,500	0	0	14.3	211.5	Carcinoma of head of the pancreas, diabetes melli- tus
			10/11	++++	++++	23.0	850	0	0	18.0	153.0	
			10/17	++++	++++	23.0	350	0	0	14.0	49.0	10/24, cholecystogastros- tomy
			10/18	++++	++++	24.0	900	12	103	15.7	141.3	
			10/22	++++	++++	23.8	1,100	Trace	Trace	13.6	157.7	
			11/7	++	+++	24.0	1,100	3	33	11.3	124.3	
			11/15	+	±	21.4	600	12	79	Trace	Trace	Obstructive jaundice
			11/18				920	12	110	0	0	
			11/19				530	Trace	Trace	0	0	
			11/21				600	6	36	0	0	
			11/24				670	12	80	0	0	
			11/25									
2 L M	64	F	9/11	++++	++++	30.0		0	11.2		Obstructive jaundice	
9/18				0		12.0						
3 A S	34	F	11/2	++	+++	31.0	1,800	0	0	13.6	244.8	Carcinoma of head of pan- creas (operation)
4 F W	71	M	11/14	++++	++++	14.0	600	0	0	7.0	42.0	Carcinoma of head of pan- creas (operation)
5 E O	30	F	3/21	±	+	34.0			480		Cholemia following chronic choolangitis with obstruc- tion of common bile duct, operation, death	
3/30			±	++	35.4			230				
4/12			0	+	32.8			450				
12/13			+++	+++	25.8							
12/15						1,700	9	153	10.5	178.5		
			1/4	++	+++	20.8	1,500	9	135	9.9	149.5	
			1/7	+++	+++	14.3						

All of these patients excreted bile acids in the urine. The amounts, however, appear to be relatively small and variable, ranging from 42 to 244.8 mg for twenty-four hours.

CASE 1—J. S., a man, aged 58, with carcinoma of the head of the pancreas, was admitted to the hospital on Oct. 9, 1927. He had had jaundice, clay colored stools and dark urine for about two weeks and sugar in the urine since the middle of August. On October 24, cholecystogastrostomy was done. The postoperative recovery was good. The cholemia and diabetic symptoms were relieved. He was discharged on December 5, with temporary improvement. When he was admitted to the hospital, the icterus index was 92.5 and the bile acids in the serum, 24 mg per hundred cubic centimeters, urobilin was absent and the bile acids, 214.5 mg for the twenty-four hour urine. During the following twelve days the icterus index increased to 141.4, but the bile acids of the blood remained unchanged. Two weeks after the operation, the icterus index dropped to 31.5, while the bile acids still remained unchanged. Four weeks after the operation, the test for bile acids in the urine was negative.

CASE 5—E. C., a woman, aged 30, had a history of jaundice of two years' duration. She had been operated on for cholecystectomy on March 12, 1925. A plastic operation on the common duct for stricture was done on March 17, a tube being used. A similar operation was performed on June 11, 1926, and again the patient was readmitted to the hospital on Jan. 2, 1928. On January 5, she was operated on for removal of the tube and reinsertion of a new tube into the common duct. She died two days after the operation. On March 21, 1927, the icterus index was 16.6 and the bile acids in the serum, 34 mg per hundred cubic centimeters. The excretion of urobilin in the urine was 480 mg for twenty-four hours. On March 30, the phenoltetrachlorophthalein test was done, and the dye retention in the blood serum after fifteen minutes was 20 per cent, and after sixty minutes, 10 per cent. The icterus index had gradually increased and reached 53.5 before her death, but the bile acids in the blood decreased to 14.3 mg. Output of the bile acids in the twenty-four hour urine was 178.5 mg on December 15 and 149.5 mg on January 4.

Cardiac Disease—In table 6 are presented three cases of cardiac disease. Of these, cases 1 and 3 showed a mild cardiac decompensation, both cases showed an icterus index below 7. Case 2 (E. B.) showed a double mitral valvular disease, with severe cardiac decompensation and an enlarged liver. The icterus index was above 10, and the indirect Van den Bergh test was positive. All of these patients presented high figures for bile acids in the serum, ranging from 22 to 33 mg per hundred cubic centimeters. Urobilin was found in the urine in all cases, and the bile acids showed a marked increase from 63.6 to 108.5 mg for twenty-four hours.

Miscellaneous Cases—In table 7 are presented five miscellaneous cases. Cases 1, 3 and 4 were cases of gastro-enteritis. In case 2 the patient had pernicious anemia and in case 5, typhoid fever.

CASE 1—A. F. gave an icterus index of 12.5, with serum bile acids of 22.2 mg per hundred cubic centimeters. Urobilin and bile acids were both present in the urine. Inflammation in the duodenum was definitely established.

TABLE 6—*Cardiac Disease*

Case	Age	Sex	D tte, 1927-28	Blood				Urine				Comment
				Icterus Index	V in den Bergh		Bile Acids, Mg per 100 Cc	Urobilin		Bile Acids		
					Direct	Indirect		Mg per 100 Cc	Mg per Vol	Mg per 100 Cc	Mg per Vol	
1 C H	12	F	12/10	7.0	0	0	33.0	47	293	10.1	63.6	Mitral insufficiency, polio myelitis
			12/15				3	15	9.2	46.9		
			12/27									
2 F B	8	F	10/2	10.0	0	+	22.0	6	36	12.0	72.0	Mitral stenosis and insuffi ciency, pericarditis acute endocarditis
			10/19	11.5	0	+	28.6	0	0	11.8	100.3	
			10/20					6	45	11.5	86.3	
			11/2	10.2	0	+	31.2	Trace	Trace	8.5	23.0	
3 C V	6	M	1/9	6.8	0	0	29.8	6	55	11.8	108.5	Mitral stenosis and insuffi ciency, subacute endocard itis, secondary anemia

TABLE 7—*Miscellaneous Cases*

Case	Age	Sex	Date, 1927-28	Blood			Urine				Comment
				Van den Bergh		Bile Acids, Mg per 100 Cc	Urobilin		Bile Acids		
				Direct	Indirect		Mg per 100 Cc	Mg per Vol	Mg per 100 Cc	Mg per Vol	
1 A F	52	M	10/ 8	±	+	22.2	12	240	8.5	170.0	Gastro enteritis
2 S B	57	M	11/28 12/ 3 12/ 4 12/ 7	0	0	16.1	Trace 0 0 0	Trace 0 0 0	Trace 0 0 0	Trace 0 0 0	Pernicious anemia in tapsy
3 W S	41	M	12/11 12/14	0	±	26.5	0 Trace	0 Trace	5.5 6.5	93.5 52.0	Chronic gastritis, periduo dentitis
4 P C	12	F	2/15	0	0	5.0	0	0	0	0	Eczema of skin, chronic enterocolitis
5 B W	27	F	12/22 1/16	0	± ±	8.5 27.5	3 0	0	Trace 4.0	Trace 24.0	Typhoid fever High fever Crisis

CASE 2—S B showed a normal icterus index and slightly increased bile acids in the serum. The urine did not contain urobilin or bile acids.

CASE 3—In W S, the icterus index was normal, while the bile acids in the blood serum were high, 26.5 mg per hundred cubic centimeters. Urobilin was not present, but bile acids were found in the urine. This patient had periduodenitis.

CASE 4—P C showed low normal figures for the icterus index and bile acids in the serum. Neither urobilin nor bile acids were found in the urine.

CASE 5—At the height of the fever in B W, the concentration of the bile acids in the blood was normal, 8.5 mg per hundred cubic centimeters, the icterus index also was normal. Two weeks later, at the crisis, bile acids in the serum increased to 27.5, and the icterus index also showed a corresponding slight increase.

COMMENT

Increased bile acids of the blood serum associated with urinary excretion of bile acids are seen in persons with cholecystitis, disease of the liver, catarrhal jaundice, obstructive jaundice and cardiac decompensation. It is common in patients with cardiac decompensation associated with a mild degree of jaundice and enlargement of the liver.

The presence of bile acids in the blood of persons with obstructive jaundice has been accepted as a fact since the early experiments of Kuhne²² and Huppert²³. More recently, Rosenthal and Wislicki,²⁴ Perlzweig and Barron²⁵ and Snell, Greene and Rowntree²⁶ obtained positive reactions for bile acids in the blood of patients or animals with obstructive jaundice. Shattuck, Kilham and I¹¹ observed in experiments with animals that phosphorus poisoning produces both a hyperbilirubinemia and an increase in the bile acids of the blood. The increase in bile acids observed after phosphorus poisoning is apparently due to a retention. We also demonstrated that an acute hemolysis increases the bilirubin of the blood serum but does not influence the concentration of bile acids.

Smyth and Whipple²⁷ reported that chloroform in remarkably small doses incapable of causing recognizable histologic injury to the

22 Kuhne, W. A Study of Jaundice, *Physiological Chemical Observation*, Arch f path Anat u Physiol **14** 310, 1858.

23 Huppert, H. The Fate of Bile Acids in Jaundice, Arch f Heilk **5** 236, 1864.

24 Rosenthal, F, and Wislicki, L. Quantitative Determination of Bile Acids in Blood, Arch f exper Path u Pharmacol **117** 8, 1926.

25 Perlzweig, W A, and Barron, E G. New Colorimetric Method for the Determination of Bile Acids in Blood, Proc Soc Exper Biol & Med **24** 23 (Dec) 1926.

26 Snell, A M, Greene, C H, and Rowntree, L G. Diseases of the Liver VII Further Studies in Experimental Obstructive Jaundice, Arch Int Med **40** 471 (Oct) 1927.

27 Smyth and Whipple (footnote 3, second reference).

liver or clinical reaction can effect a decrease in the concentration of bile acids in bile from fistulas. In large doses, phosphorus also has a depressant effect on the output of bile acid in bile from fistulas. Moreover, Foster, Hooper and Whipple²⁸ observed that a functionally deficient liver (Eck fistula) produces less than one-half the normal amount of bile acids during a standard diet period. These authors concluded that such observations present more evidence to substantiate the theory that the bile acids are produced by the liver and not elsewhere in the body. However, it is equally logical to attribute the diminished excretion of the bile acids in the bile to a retention by the liver.

It is of interest to note that the changes in the concentration of bile acids in the blood do not bear any relation to variations in bilirubin. This is seen in tables 2, 6 and 7. Smyth and Whipple found that the injury to the liver produced by liver poisons sometimes depressed, and at other times was without influence on, the excretion of bile pigments. Apparently, then, whatever part the liver plays in bile acid metabolism may in experiments and pathologic conditions be affected independently of its function in bile pigment metabolism. Moreover, it appears possible that the diminished excretion of bile acids in the bile after injury to the liver may be due to a retention and not to a diminished formation.

Acute obstructive or catarrhal jaundice produced a rapid rise in the bilirubin of the blood serum and a marked increase in bile acids associated with urinary excretion of bile acids and bile pigments. In chronic obstructions (table 5), however, the increase in bile acids in the blood is much less, reaching only from three to four times the normal. This smaller concentration of bile acids in the blood in chronic obstructions may be attributed to impairment of the ability of the liver to produce bile acids after long obstructions. However, there is another possible explanation. The production of bile acids in the body is limited. Normally, the bile acids are excreted by way of the bile into the intestine, reabsorbed and again circulated, thus keeping the bile acid in the body at a constant amount. In persons with obstructive jaundice of long standing, however, there is a continuous excretion of bile acids by the kidney, which, of course, cannot be reabsorbed, thus depleting the store of bile acids in the body.

Brakefield and Schmidt²⁹ produced obstructive jaundice in dogs by ligation and subsequent resection of the common bile duct. They noted that the production of the jaundice was followed by a urinary excretion of bile acid and bile pigment, but the output of bile acid decreased and

28 Foster, Hooper and Whipple (footnote 3, first reference)

29 Brakefield, J. L., and Schmidt, C. L. A. Studies on the Synthesis and Elimination of Certain Bile Components in Obstructive Jaundice, *J. Biol. Chem.* 67: 523 (Feb.) 1926

finally became small in quantity. An injection of taurocholic acids led to an increased excretion of this substance. Moreover, it was found that the ability of the jaundiced dog to detoxicate benzoic acid was markedly diminished, and microscopic section of the livers showed extensive morphologic changes. According to the observations of these authors, the diminished excretion of bile acids was due to an impairment of the ability of the liver to produce the bile acids. J. S. (case 1, table 3) and J. S. (case 1, table 5) had high bile acids in the blood and urinary excretion of bile acids. The concentration of bile acids in the blood decreased on subsequent examinations but did not approach the normal level, although the urinary excretion of bile acids gradually diminished and finally disappeared. In E. C. (case 5, table 5), who had long standing obstructive jaundice, the concentration of bile acids in the blood was 34 mg per hundred cubic centimeters. Ten months later, the amount of bile acids in the blood was still 20.8 mg per hundred cubic centimeters above the normal, while the output of bile acids in the urine was 149.5 mg for twenty-four hours. These facts cannot be explained by the theory of Brakefield and Schmidt.

In persons with catarrhal jaundice (table 4) are seen marked variations in the excretion of urobilin, in some instances ranging from a negative reaction to more than 1 Gm in twenty-four hours. Wallace and Diamond³⁰ and Shattuck, Killian and I¹¹ reported great variations in excretion of urobilin in persons with catarrhal jaundice, the curve showing peaks of large amount and dropping off to a scanty excretion or a negative reaction within twenty-four hours, with a prompt subsequent rise. However, the urobilin never remains permanently absent from the urine in persons with catarrhal jaundice. In obstructive jaundice (table 5), the urobilin was absent or was excreted in minute amounts. When the obstruction is relieved, urobilin reappears in the urine. If the excretion of urobilin in the urine is to be utilized as an aid in the differential diagnosis between obstructive and catarrhal jaundice, the determinations of urobilin in the urine must be continued over a period of not less than five days.

SUMMARY

The bile acids of normal blood serum varied from 5 to 12 mg per hundred cubic centimeters, estimated as sodium glycocholate. The average was 7 mg per hundred cubic centimeters.

The urine of normal subjects showed a negative reaction for bile acids.

³⁰ Wallace, A. B., and Diamond, J. S. The Significance of Urobilin in the Urine as a Test for Liver Function with a Description of a Simple Quantitative Method for Its Estimation, *Arch Int Med* 35:698 (June) 1925.

Patients with cholecystitis, disease of the liver, catarrhal jaundice, obstructive jaundice, cardiac decompensation and duodenitis showed a marked increase in the bile acids of the blood serum, accompanied by urinary excretion of bile acids. The amount of bile acids in the urine, however, appears to be relatively small and extremely variable.

The changes in the concentration of bile acids in the blood do not bear any relation to variation in bilirubin of the blood.

The bile acids appear in the urine when the concentration of bile acids in the blood serum exceeds 20 mg per hundred cubic centimeters.

Acute obstructive or catarrhal jaundice produced a rapid rise in the bile acids of the blood serum from about five to seven times the normal figure. In chronic obstructions, however, the increase in bile acids in the blood is much less, to only three or four times the normal. This smaller concentration of bile acids in the blood in chronic obstructions may be explained thus:

The production of bile acids in the body is limited. Normally, they are excreted by way of the bile into the intestine, then they are reabsorbed and again circulated, thus keeping the bile acids in the body at a constant amount. In obstructive jaundice of long standing, however, there is a continuous excretion of bile acids by the kidney, which, of course, cannot be reabsorbed, thus depleting the store of bile acids in the body.

DISTRIBUTION OF BLOOD SUGAR BETWEEN CORPUSCLES AND PLASMA IN DIABETIC AND IN ALIMENTARY HYPERGLYCEMIA*

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ST LOUIS

It has been demonstrated that the generally accepted view of an equal or nearly equal distribution of sugar between corpuscles and plasma in human blood is erroneous¹. The evidence was based on true sugar values, obtained as the difference between apparent sugar (total reduction) and nonsugar-reducing substances.

It has long been known that nonfermentable substances constitute a part of the sugar values estimated by the usual reduction methods, but—owing to reasons set forth elsewhere²—these substances eluded quantitative determination to such an extent that some investigators asserted that almost half of the reduction of protein-free filtrates of normal blood is due to nonfermentable constituents, while others denied altogether the existence of such substances. A simple procedure devised by me, involving fermentation by means of thoroughly washed yeast, permits the rapid and complete removal of fermentable sugars from blood and other biologic fluids, and thus the accurate determination of nonfermentable reducing substances or “residual reduction.”

Two interesting observations have resulted from the estimation by this method of the reducing nonsugars in human blood, one, the remarkable constancy of the amount, and the other, the unequal distribution of these substances between corpuscles and plasma. The average quantity of reducing nonsugars is 40 mg per cent in corpuscles, while it is only 8 mg per cent in plasma. From this it follows that the ratio, $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$, a convenient expression for the distribution of sugar, is grossly distorted by the reducing nonsugar fractions included in the apparent sugar values. This ratio, as expressed by former investigators, was $\frac{\text{apparent corpuscle sugar}}{\text{apparent plasma sugar}}$, whereas the correct formulation is $\frac{\text{true corpuscle sugar}}{\text{true plasma sugar}} = \frac{\text{apparent corpuscle sugar}-40}{\text{apparent plasma sugar}-8}$.

The fallacy arising from the use of apparent sugar values is brought out in a previously published report of the observations on thirty-six

* From the Laboratory of the Jewish Hospital of St. Louis.

1 Somogyi, Michael. The Distribution of Sugar in Normal Human Blood, *J Biol Chem* **78** 117, 1928.

2 Somogyi, Michael. Reducing Nonsugars and True Sugar in Human Blood, *J Biol Chem* **75** 33, 1927.

specimens of normal human blood,¹ which yielded the following results

	Lowest	Highest	Average
True distribution ratio	0.66	0.95	0.77
Apparent distribution ratio	0.96	1.35	1.10

According to the apparent sugar values 100 cc of corpuscles contain, on an average, 1.1 mg of sugar for each milligram in 100 cc of plasma, in conformity with the accepted view of a nearly equal distribution. The true sugar values, however, show a much lower relative sugar content in the corpuscles, namely 0.77 mg for each milligram in an equal volume of plasma. The error in the distribution ratio, owing to the acceptance of apparent sugar as true sugar, is $\frac{(1.10-0.77)100}{0.77} = 43$ per cent.

TABLE 1—*Influence of the Blood Sugar Level on the Discrepancies Between the Apparent and True Distribution Ratios*

True Sugar, Mg per 100 Cc of			True Ratio Corpuscle Sugar to Plasma Sugar	Apparent Sugar,* Mg per 100 Cc of			Apparent Ratio Corpuscle Sugar to Plasma Sugar
Blood	Corpuscles	Plasma		Blood	Corpuscles	Plasma	
9	7.5	10	0.75	23	47.5	18	2.64
17.5	15	20		41.5	55	28	1.96
35	30	40		59	70	48	1.46
84	72	96		108	112	104	1.08
175	150	200		199	190	208	0.92
263	225	300		287	265	308	0.86
350	300	400		374	340	408	0.84
438	375	500		462	415	508	0.82

* Apparent blood sugar = true blood sugar + 24, apparent corpuscle sugar = true corpuscle sugar + 40, apparent plasma sugar = true plasma sugar + 8

The discrepancy between the apparent and true ratio is variable, its magnitude depending mainly on the concentration of sugar in blood. In order to illustrate this relationship a possible series of specimens of blood will be considered in which the true distribution ratio is uniformly 0.75 and the corpuscle volume is 50 per cent, the reducing nonsugars are represented by the average values of 40 and 8 mg per cent in the corpuscles and in the plasma, respectively, while the blood sugar varies from extremely low to extremely high concentrations. Table 1 shows the extent of the disguising effect of the reducing nonsugars on the distribution ratio at various blood sugar levels. The same is shown graphically in chart 1, wherein the curves were constructed by plotting distribution ratios against blood sugar values.

It is evident that the lower the blood sugar concentration the more pronounced is the discrepancy between the two ratios, that is, the more misleading becomes the apparent ratio. Especially changes in the direc-

tion of hypoglycemia entail a sudden rise in the apparent ratio. At a normal fasting sugar level of 108 mg per hundred cubic centimeters a nearly equal distribution is found, but as the blood sugar goes down to 59 mg per hundred cubic centimeters, the apparent ratio indicates 1.46 per hundred cubic centimeters of corpuscle sugar for 1 mg per hundred cubic centimeters of plasma sugar, and at 33 mg per hundred cubic centimeters of blood sugar, the apparent ratio rises to 2.64, whereas the true ratio is identical at all of these blood sugar levels. Ultimately, as the blood sugar progressively diminishes, the apparent ratio approaches the maximum value of 5.1, a limit reached only when the true sugar becomes zero, and the entire

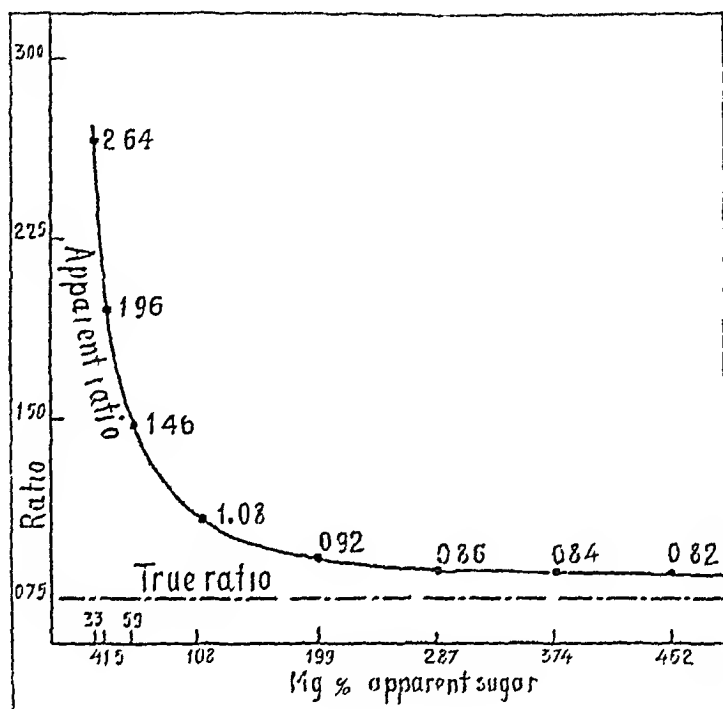


Chart 1—The ratio expressing the distribution of blood sugar between corpuscles and plasma is distorted by the reducing nonsugars (residual reduction), especially at lower blood sugar levels

reduction is due to reducing nonsugars. On the other hand, as the blood sugar rises to hyperglycemic levels, the divergence between the apparent and the true ratio gradually decreases, and the two values asymptotically approach identity.

As can be seen, the apparent ratio simulates changes in the distribution of the blood sugar, when actually there are none. As previous investigators have based some interesting conclusions concerning the distribution of blood sugar under various conditions on apparent sugar values, I considered it desirable to study such questions in the light of true sugar values.

John³ and Wiechmann⁴ observed a nearly equal distribution of the sugar between corpuscles and plasma in the blood of fasting normal persons, but in the blood of diabetic patients they found a higher sugar content in the plasma than in the corpuscles. Both authors believe that some constituent of the diabetic plasma inhibits the permeability of the erythrocytes for dextrose. Loewi⁵ accepts this view, and claims to have demonstrated in the plasma of diabetic patients the existence of a hormone (glycemin) which lowers the "sugar binding or sugar fixing ability" of the erythrocytes.

TABLE 2—*Distribution of Sugar in Blood of Diabetic Patients*

Number	Apparent Sugar, Mg in 100 Cc of		Reducing Nonsugars, Mg in 100 Cc of		True Sugar, Mg in 100 Cc of		Ratio Corpuscle Sugar	
	Cor- puscles	Serum	Cor- puscles	Serum	Cor- puscles	Serum	Serum Sugar	
							For Apparent Sugar	For True Sugar
1	231	259	43	8	188	251	0.90	0.75
2	161	179	38	8	123	171	0.90	0.70
3	174	195	44	8	130	187	0.90	0.70
4*	215	231	51	10	164	221	0.93	0.74
5	148	159	38	9	110	150	0.93	0.73
6	220	229	39	8	181	221	0.96	0.82
7	169	162	43	7	126	155	1.04	0.81
8	191	191	44	13	147	178	1.00	0.83
9	208	225	37	8	171	217	0.92	0.79
10	243	267	44	14	199	253	0.99	0.79
11	200	227	35	8	165	219	0.88	0.75
12†	287	302	42	8	245	294	0.95	0.83
13	140	150	38	8	102	142	0.93	0.72
14	137	137	38	8	99	129	1.00	0.77
15	144	142	40	8	104	134	1.01	0.77
16	158	166	37	9	121	155	0.95	0.78
17†	251	290	39	8	212	282	0.90	0.75
Lowest							0.85	0.70
Highest							1.04	0.83
Average							0.95	0.77

* Specimen of blood withdrawn thirty minutes after the ingestion of 100 g of dextrose.

† Specimen of blood withdrawn two hours after the ingestion of 100 g of dextrose. The other specimens were obtained before breakfast.

In a series of experiments in which I examined the blood of seventeen diabetic patients, I obtained results—given in table 2—that fully bear out the view of John and of Wiechmann, as far as the apparent sugar values are concerned. The average apparent ratio is 0.95 as against 1.10 in normal blood, indicating that the relative sugar content of the corpuscles is 15 per cent lower in blood from diabetic patients than in

3 John, H. J. Distribution of Sugar in Whole Blood, Plasma and Corpuscles, Permeability of Red Corpuscles for Sugar in Diabetic and Nondiabetic Cases, *Arch Int Med* **31** 555 (April) 1923.

4 Wiechmann, E. Zur Frage der Permeabilität der roten Blutkörperchen für Traubenzucker unter besonderer Berücksichtigung des Diabetes, *Ztschr f d ges exper Med* **41** 462, 1924.

5 Loewi, O. Glvkamin und Insulin, *Klin Wchnschr* **6** 2169, 2173, 2175, 1927.

that from normal subjects. The true sugar values, however, disclose an average distribution ratio of 0.77, the same as was found in normal blood.

In an endeavor to obtain the most conclusive results possible, I chose for my experiments only patients with more or less severe diabetes. In five cases, sugar tolerance tests were performed by following the changes in the blood sugar level during three hours after the administration of 100 Gm of dextrose. These tests, presented in table 3, fairly characterize the condition of these patients, at the same time, they demonstrate the absence of any connection between the severity of the diabetes and the distribution of the blood sugar. In case 1, the patient, a "total" diabetic, had a distribution ratio of 0.75, the same as in case 17, the mildest of the five cases, while in case 6, with a tolerance curve closely resembling that in case 1, the high ratio of 0.83 was found. These were variations not in the least different from those occurring in normal

TABLE 3—*Sugar Tolerance Tests*

Time After Ingestion of 100 g of Dextrose	No 1	No 4	No 6	No 12	No 17
	Mg Sugar in 100 Cc of Blood				
0 (fasting)	265	151	240	145	140
30 minutes	385	230	405	225	233
60 minutes	459	313	440	275	324
120 minutes	484	356	504	295	272
180 minutes	472	353	471	247	194
Distribution ratio	0.75	0.74	0.82	0.83	0.75

specimens, and it is safe to conclude that diabetes mellitus does not have any effect on the distribution of sugar between corpuscles and plasma, in other words, it does not influence the ability of the corpuscles to take up (fix, bind) dextrose.

Careful inspection of the experimental data of the authors just quoted leads one to surmise that their unawareness as to the rôle of the reducing nonsugars is not the exclusive cause responsible for the conflict between their results and those reported in this article. Wiechmann, for instance, found 13 and 15 mg per hundred cubic centimeters of apparent sugar in the blood corpuscles of a healthy man. As the reducing nonsugars in corpuscles alone yield considerably higher values by the method of Folin and Wu—the one employed by Wiechmann—such low values are obviously due to some error in analytic technique.

The distribution of blood sugar in hyperglycemic conditions of nondiabetic genesis has been studied by several workers. In 1912, Hober⁶ reported that in alimentary and in epinephrine hyperglycemia

6 Hober, R. Ueber die Verteilung des Blutzuckers auf Körperchen und Plasma, *Biochem Ztschr* 45 206, 1912.

the increment in the blood sugar goes eminently to the plasma, that is, the relative sugar concentration in the corpuscles is lowered Tachau,⁷ Wishart,⁸ Folin and Berglund⁹ and Rona and Sperling¹⁰ found a relatively greater increase in the concentration of the plasma sugar during alimentary hyperglycemia Loewi⁵ said that he believed he had shown the opposite of this, namely, a substantial and progressive increase in the "sugar fixing ability" (relative sugar content) of the corpuscles during three hours following the administration of sugar by mouth

TABLE 4—*Showing that Changes in the Level of the Blood Sugar do not Affect the Distribution Ratio*

No	Case	Apparent Sugar, Mg in 100 Cc of		True Sugar, Mg in 100 Cc of		Ratio, Corpuscle Sugar	
		Cor- puscles	Serum	Cor- puscles	Serum	Serum Sugar	
						For Apparent Sugar	For True Sugar
1	Normal man, fasting	112	99	76	90	1.13	0.84
	30 minutes after dextrose	184	184	148	175	1.00	0.85
	180 minutes after dextrose	77	59	41	50	1.31	0.82
	210 minutes after dextrose	83	66	49	58	1.26	0.84
2	Normal man, fasting	105	101	68	94	1.04	0.72
	30 minutes after dextrose	130	129	93	122	1.00	0.77
	210 minutes after dextrose	87	73	50	66	1.19	0.76
3	Normal man, fasting	111	89	75	81	1.25	0.93
	30 minutes after dextrose	178	167	142	159	1.07	0.90
	180 minutes after dextrose	93	74	57	66	1.26	0.86
4	Normal man, fasting	110	103	72	93	1.07	0.77
	180 minutes after dextrose	121	110	83	100	1.10	0.83
5	Normal woman, fasting	124	128	84	120	0.98	0.70
	30 minutes after dextrose	181	205	141	197	0.89	0.72
6	Normal man, fasting	108	110	69	101	0.98	0.68
	60 minutes after dextrose	150	161	109	154	0.93	0.71
7	Diabetic, fasting	140	150	102	142	0.93	0.72
	180 minutes after dextrose	304	358	266	350	0.85	0.76
8	Diabetic, fasting	137	137	99	129	1.00	0.77
	60 minutes after dextrose	230	265	192	257	0.87	0.75

My observations concerning the conditions in alimentary hyperglycemia, and the ensuing hypoglycemia—which is thought to be essentially identical with insulin hypoglycemia—are recorded in table 4. These experiments were carried out on six healthy and two diabetic subjects. The former received 120, the latter 90 Gm of dextrose by mouth after blood had been withdrawn during the fasting condition.

7 Tachau, H. Ueber die Verteilung des Blutzuckers auf Blutkörperchen und Plasma, *Ztschr f klin Med* **79** 421, 1914

8 Wishart, M. B. The Permeability of Blood Corpuscles to Sugar, *J Biol Chem* **44** 563, 1920

9 Folin, O., and Berglund, H. Some New Observations and Interpretations with Reference to Transportation, Retention and Excretion of Carbohydrates, *J Biol Chem* **51** 213, 1922

10 Rona, P., and Sperling, M. Ueber die Verteilung der Glucose auf Plasma und Blutkörperchen, *Biochem Ztschr* **175** 253, 1926

Further specimens of blood were obtained at intervals after the ingestion of the sugar. The results require little comment. The apparent sugar values simulate changes in the distribution of the blood sugar, which are in accord with the conclusions of previous workers. Experiment one in table 4—graphically represented in chart 2—is an apt example to illustrate this. When, during the absorption of dextrose, the blood sugar rises to a hyperglycemic level, the concentration of the plasma sugar seemingly increases more rapidly than that of the corpuscle sugar, and the apparent ratio indicates a drop of 13 per cent in the relative sugar content of the corpuscles. Again, as the blood later recedes to a

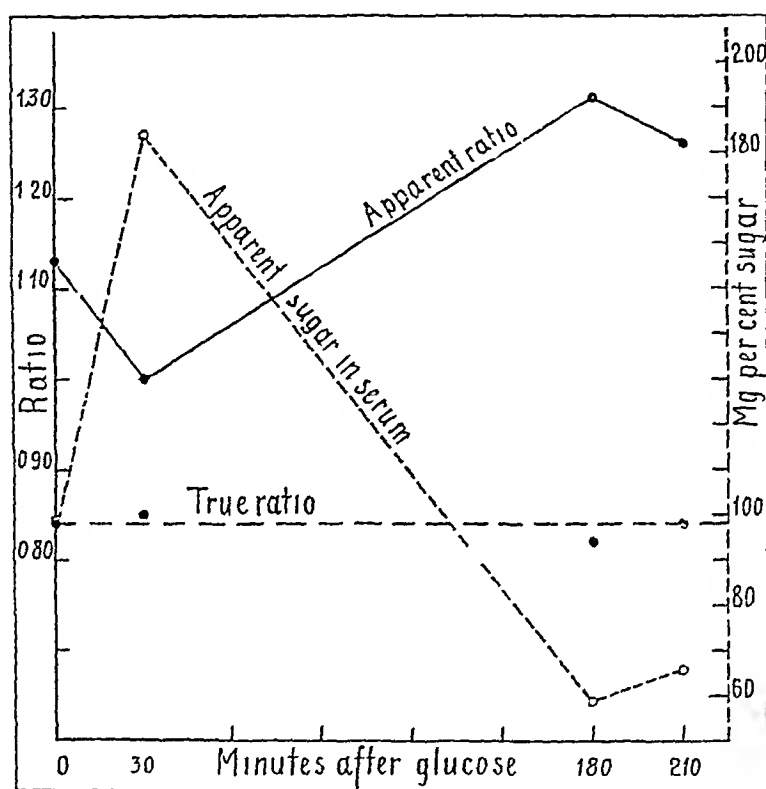


Chart 2—True sugar values show no alteration in the distribution of blood sugar during alimentary hyperglycemia, while apparent sugar values simulate substantial changes

hypoglycemic level, the plasma appears to lose of its sugar content faster than the corpuscles, and—as expressed by the apparent ratio—the relative concentration of the corpuscle sugar is increased by 31 per cent. According to the evidence of the true sugar values, however, the ratio of distribution remains largely unchanged throughout the rise and fall of the blood sugar concentration in all of the cases given in table 4, regardless of the normal or diabetic condition.

According to Rona and Sperling,¹⁰ during the decline of the blood sugar concentration subsequent to alimentary hyperglycemia, the corpuscles lose sugar more rapidly than the plasma, often showing an

abruptly steep drop. My observations are contrary to this even in regard to apparent sugar values. Rona and Sperling derived their conclusion from two experiments on a single human subject, and chiefly from observations on rabbits that were given perorally 15 Gm, in one case 30 Gm, of dextrose dissolved in from 50 to 100 cc of water. Their results are so inconsistent and conflicting among themselves that an interpretation of their data in any direction appears to be more or less arbitrary.

Loewi's work³ concerning alimentary hyperglycemia is at a decided variance to the results of all the investigators quoted as well as to my own. Loewi claims that the relative sugar concentration of the corpuscles (sugar-fixing ability) in dogs and rabbits rises and declines in a remarkable parallelism with the concentration of the blood sugar. In nondiabetic human subjects, too, the concentration of the corpuscle sugar rises more rapidly than that of the plasma sugar, but during the decline of the blood sugar level the corpuscles give up their sugar content so much more slowly than the plasma that the relative sugar concentration in the corpuscles is at a maximum three hours after the peroral administration of dextrose, when the concentration of the blood sugar had already receded to its lowest level. My observations as shown in chart 2, are in a diagonal contrast to those of Loewi. The curve of the apparent distribution ratio, instead of being parallel to the curve of the plasma sugar (which largely follows the course of the blood sugar), is more of a mirror image to it. In a subsequent paper, dealing with the influence of insulin on the distribution of blood sugar, I shall revert to the discussion of Loewi's observations, which he correlates with effects of endogenous insulin.

SUMMARY

- 1 The distribution of blood sugar between corpuscles and plasma can be determined only from true sugar values. The substitution of apparent sugar for true sugar leads to erroneous conclusions.

- 2 The relative sugar content of corpuscles is the same in blood of diabetic and nondiabetic subjects, thus, the conclusion that the sugar fixation by corpuscles is inhibited in the blood of diabetic patients (Wiechmann, Loewi) is erroneous.

- 3 The distribution of the sugar is unaffected by changes in the blood sugar level caused by alimentary factors.

THE EFFECT OF PARATHYROID EXTRACT ON CERTAIN FACTORS UNDERLYING THE PRODUCTION OF EDEMA¹

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AND

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PHILADELPHIA

It is generally conceded that in several types of edema there is some disturbance in the inorganic ion balance of the body. This is particularly true of edema associated with various forms of renal disease. Whether this imbalance as evidenced by retention of salts, particularly sodium chloride, within the tissues, plays a primary or a secondary rôle is a subject much disputed. The difficulty, if not impossibility, of reproducing edema experimentally has delayed the solution of this problem.

Experimental studies indicate that, apart from the comparatively simple form due to lymphatic obstruction, the production of edema is dependent on several factors, the individual importance of which varies in different instances. The chief of these may be enumerated as follows: (1) increased capillary permeability, (2) alterations in osmotic pressure, and (3) increased affinity of tissue colloids for water. The exact relation of the retention of salt to these phenomena and to the accumulation of fluid in the tissues has been the subject of prolonged investigation.

Edema may be classified as inflammatory and noninflammatory and may be considered under these headings.

RESULTS OF PREVIOUS INVESTIGATIONS

Under normal conditions, the wall of the capillary acts as a semi-permeable membrane, allowing free diffusion of water and certain crystalloids, such as urea, and a limited diffusion of other crystalloids. It is impermeable to most colloids. It has been demonstrated, however, that normally a variation in permeability exists in different organs. Starling¹ showed that whereas the lymph flowing from the lower extremities had a protein content of from 2 to 4 per cent, that from the liver contained from 6 to 8 per cent. The work of Krogh² has thrown considerable light on this subject. He has shown³ that a definite

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1 Starling, E. H. The Physiological Factors Involved in the Causation of Dropsy, *Lancet* **1** 1267 (May 9) 1896.

2 Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922.

3 Krogh, A., and Harrop, G. A. Some Observations on Stasis and Edema, *J. Physiol.* **54** 125, 1920-1921.

sequential relationship exists between stimulation, dilatation and increased permeability of the capillaries, and that every muscular effort results in dilatation of the capillaries. Hence, there is a constant alteration in permeability in response to the needs of the tissue, probably dependent on the local accumulation of carbon dioxide, lactic acid and other metabolic products.

The high protein content of inflammatory exudates is an indication of an increase in the permeability of the walls of the capillaries. Oswald⁴ stated, in evidence of this fact, that the walls of the capillaries of inflamed areas are permeable, not only to albumin and pseudoglobulin, but also to euglobulin and fibrinogen, the viscosity of which is relatively high. The factor of permeability, however, although of great importance, is not the only one involved. The accumulation of products of the disintegration of tissue at the site of inflammation may result in dilatation of the capillaries and in increased permeability, as proposed by Krogh. In addition, Schade⁵ has demonstrated in these areas the development of an extremely high osmotic pressure and an increase in hydrogen ion concentration. Either of these conditions may be responsible for the local accumulation of fluid, the former through the operation of the forces of osmosis, the latter through the increase in the capacity for hydration of the tissue colloids accomplished by the increased acidity. The latter factor, the significance of which was developed chiefly by Fischer,⁶ will be considered later.

The influence of inorganic ions, particularly sodium, potassium and calcium, on the permeability of the membranes of the cells is well known, normal permeability being dependent to a considerable degree on the presence of a normal balance between the inorganic ions in the fluid which bathes the cell. Calcium definitely diminishes the permeability of the cell. In fact, Loeb⁷ attributes the general inhibiting action of the calcium ion to this diminution in permeability. Osterhout⁸ believed that sodium and calcium combine with some constituent of the cell, and that the permeability varies according to the relative proportion in which these two combinations of the constituents of the cell are present.

4 Oswald, A. Ueber den Chemismus der Entzündung, *Ztschr f exper Path u Therap* 8 226, 1910

5 Schade, H. Die Molekular-pathologie in ihren Verhältnis zur zellular Pathologie und zum klinischen Krankheitsbild am Beispiel der Entzündung, *München med Wchnschr* 71 1, 1924

6 Fischer, M. H. Oedema and Nephritis, ed 3, New York, John Wiley & Sons, 1921

7 Loeb, J. The Influence of Electrolytes on the Electrification and Rate of Diffusion of Water through Collodion Membranes, *J General Physiol* 1 717, 1918-1919

8 Osterhout, W. J. V. Antagonism and Permeability, *Science* 45 97, 1917

Hamburger⁹ stated that the relation of calcium, sodium and potassium ions in a perfusing fluid is the determining factor in the production of edema, the calcium ions tend to make the capillaries impermeable, at the same time causing their constriction

Investigation of the effect of treatment with calcium on experimentally produced inflammatory edema has yielded somewhat contradictory results Januschke¹⁰ found that the typical inflammatory reaction produced by mustard oil was prevented by the previous administration of calcium salts Rosenow¹¹ found that calcium and epinephrine acted in a similar manner in inhibiting the formation of inflammatory exudates Negative results have been reported by other investigators, and it is probable, as suggested by Loeb,¹² that the difference in amount and proportion of calcium employed may account for the variable results obtained In general, the experimental observations seem to indicate that calcium is much more effective in preventing the full development of inflammatory edema than in influencing an already existing process

Calcium chloride in large doses has been used clinically in the treatment of patients with acute inflammatory conditions, particularly serofibrinous pleurisy Oriani¹³ and Thoné¹⁴ reported good results, with subsidence of the fever and resorption of the effusion According to Blum¹⁵ and others, calcium chloride diminishes the sodium of the blood and prevents it from migrating from the blood into the inflammatory area As the current of water follows sodium, the accumulation of fluid ordinarily accompanying the inflammatory process is inhibited However, it would appear probable that whatever effect calcium has on this type of edema, it is exerted largely through its influence on the permeability of the cell

NONINFLAMMATORY EDEMA

When one turns to the consideration of noninflammatory edema, as typified by that accompanying cardiac and renal disease, an apparently different problem is encountered The fact that the fluid of edema in

9 Hamburger, R J Ueber die bedeutung der Kalium und Calciumionen fur das kunstliche Oedem und fur die Gefassweite, *Biochem Ztschr* **129** 153, 1922

10 Januschke, H Ueber Entzündungshemmung, *Wein, klin Wchnschr* **24** 869, 1913

11 Rosenow, G Der Einfluss parenteraler Calcium zufuhr auf die Durchlassigkeit der Gefasswand, *Ztschr f d ges exper Med* **4**:427, 1916

12 Loeb, L Edema, *Medicine* **2** 190, 1923

13 Oriani, F Calcium Chloride in Treatment of Effusions, *Clin med ital* **56**:475 (Dec) 1925

14 Thoné Calcium Chloride in Exudative Pleurisy, *Arch méd belges* **78**:1 (Jan) 1925

15 Blum, L, Aubel, E, and Hausknecht, R Action diuretique des sels de calcium mecanisme de cette action, *Compt rend Soc de biol* **85** 950, 1921

these conditions is relatively low in protein indicates that increased permeability of the capillaries probably plays a relatively minor part in its causation. However, there is considerable evidence to suggest that this factor is involved to some degree. The work of Morawitz and Denecke¹⁶ suggests that in glomerular nephritis, typhoid, scarlet fever, purpura and acute endocarditis there is a state of increased permeability of the capillaries. They assumed this to be due to toxic injury of the vessels. However, in cardiac edema they found the permeability to be normal. Recently, Skelton¹⁷ found that following hemorrhage various tissues give up water to the blood stream, in proportion to the normal variation in the permeability of the capillaries, this was demonstrated in different organs by Starling,¹ thus, the liver lost the greatest amount of water per unit of mass, the skin and intestines a lesser amount and the muscles the least amount.

Cohnheim¹⁸ believed that in nephritis the vascular injury with resultant increase in permeability is secondary to retention of toxic substances in the blood stream, but Senator¹⁹ considered that the vascular and renal injury are due to the same cause. Wells²⁰ said that it is probably better to consider the toxic effect as applying to all cells rather than merely to capillaries. Apparently, the edema cannot be explained by the mere diminution of the functional area of the kidney in nephritis, for neither bilateral nephrectomy nor ureteral occlusion necessarily results in accumulation of fluid within the tissues. Neither can cardiac edema be satisfactorily demonstrated as being due entirely to increase in venous pressure dependent on myocardial failure. The great bulk of accumulated evidence seems to indicate that the mechanism of osmosis and altered affinity of the tissue colloids for water are the factors chiefly concerned in these types of edema.

The importance of the retention of salt in the causation of edema was emphasized particularly by Widal²¹. Although many investigators believe this retention to be the primary factor, others consider it secondary to the accumulation of fluid in the tissues. Fischer⁶ held that the primary factor is an increase in the acidity of the tissue, which causes an increased affinity of the tissue colloids for water, with resulting

16 Morawitz, R, and Denecke, G. Ueber Quellungs-vorgänge in subcutanen Gewebe, *Biochem, Ztschr* **127** 47, 1922

17 Skelton, Harold. The Storage of Water by Various Tissues of the Body, *Arch Int Med* **40** 140 (Aug) 1927

18 Cohnheim, J, and Lichthelm, L. Ueber Hydrämie und hydramisches Oedem, *Virchows Arch f path Anat* **69** 106, 1877

19 Senator, H. Ueber die Wassersucht bei Nierenkrankheiten, *Klin Wchn-schr* **33** 165, 1895

20 Wells, H G. *Chemical Pathology*, ed 5, Philadelphia, W B Saunders Company, 1925, p 387

21 Widal, F. La cure de dechlorination, *Bull et mem Soc d hôp de Paris* **20** 773, 1903

retention of salts, particularly sodium chloride. He stated that the proportion of water present in any cell or fluid containing colloids is determined by the character of the colloids, the reaction of the solution and the nature of its electrolyte content. The fact that the retention of salt often occurs in fevers without edema would suggest that some additional condition is necessary. The work of Cohnheim and Lichtheim,¹⁸ and of Muller²² and many others indicates that increased permeability of the capillaries may be an essential factor.

Considerable light has been thrown on certain phases of this problem by McClure and Aldrich.²³ They found that a small amount of physiologic solution of sodium chloride injected intradermally is entirely taken up by normal tissues in from sixty to eighty minutes. In tissues which are the site of edema or in which a tendency to edema is present, as in nephritis and cardiac disease, the injected fluid disappears more rapidly. This fact is interpreted as indicating an increase in the affinity of the tissues for water, supporting Fischer's contention that variations in the capacity of hydration of tissue colloids play a major rôle in the production of cardiac and renal edema.

The exact mechanism of the action of the various cations in this connection is not clearly understood. However, certain facts have been critically demonstrated. In many cases of edema, particularly those occurring in association with nephritis, there is retention of sodium within the tissues. Whether this retention is primary or secondary to the accumulation of fluid is an open question. However, there cannot be any doubt that it is an essential factor, for in a large proportion of such cases restriction of the intake of sodium is followed by increased elimination of this element chiefly by the kidneys, a greatly increased fluid output and a diminution in the edema.

Naturally, as a result of the known antagonistic actions of sodium and calcium in the body, the effect of the latter on the process of edema has been studied extensively. In general, it has been found, although some contradictory results are reported, that the administration of calcium salts in large doses produces an effect on edema comparable to that obtained by the restriction of the intake of sodium.

Maase and Zondek²⁴ reported extremely favorable results from the use of calcium therapy in the peculiar condition known as war edema, probably a nutritional disorder. Hulse²⁵ gave calcium salts

²² Muller, F. Morbus brightii, Verhandl d deutsch path Gesellsch 9 64, 1905

²³ Aldrich, C. A., and McClure, W. B. Intradermal Salt Solution Test, J A M A 82 1425 (May 3) 1924

²⁴ Maase, C., and Zondek, H. Das Kriegsodem, Klin Wchnschr 54-861, 1917

²⁵ Hulse, W. Ueber den Einfluss der Kalksalze auf Hydrops und Nephritis, Centralbl f innere Med 41.441, 1920

orally in large doses to patients with nephritis and noted a marked reduction in the edema. Many similar results have been reported with various explanations for the mode of action of calcium in this type of edema. It does not seem possible that the effect here can be attributed to the decrease in the permeability of the cell, which is probably of major importance in the control of inflammatory edema. The work of Skelton¹⁷ is of great interest in this connection. He found, as stated previously, that after hemorrhage the tissues gave up fluid to the blood stream in relative proportion to the permeability of the capillaries in the respective organs as demonstrated by Starling, namely, the greatest relative loss occurred in the liver and the least in the skin and muscles. On the other hand, following the intravenous injection of a 2.4 per cent solution of calcium chloride, water was abstracted from all tissues, but the greatest loss occurred in the skin, where the permeability of the capillaries is relatively low. This fact, in the light of the observation by Schade²⁶ that the subcutaneous tissues possess an especial predilection for sodium chloride, seems to have a particular bearing on the problem of the therapeutic action of calcium in noninflammatory edema.

Fischer⁶ stated that the edema which may follow the administration of sodium chloride or sodium bicarbonate is due to the replacement of calcium and magnesium in the tissues by sodium, for sodium proteins have a much greater affinity for water than calcium proteins. Frey²⁷ believed that the increased elimination of the fluid of edema by the kidneys may be explained by the fact that calcium is eliminated chiefly through the intestines, while the anion is excreted through the kidneys and draws with it the sodium ion. Whatever the true explanation may be, it is evident that the mutual physiologic antagonism of the sodium and the calcium ion has an important bearing on the problem of edema.

PRESENT INVESTIGATION

The present study was undertaken for the purpose of observing the effect of an increase in available circulating calcium on (1) the development of inflammatory edema and (2) the affinity of the tissue colloids for water.

METHODS

The increase in calcium was accomplished by the intramuscular administration of parathyroid extract²⁸. In our previous studies, it was noted that from 15 to 20

26 Schade, H. Untersuchungen zur Organfunktion des Bindegewebes, das Quellungsvermögen des Bindegewebes in der Mannigfaltigkeit seiner Erscheinungen, *Ztschr f exper Path u Therap* **14** 1, 1913.

27 Frey, W. Die Einwirkung von Brom auf die Ausscheidung von Wasser und Kochsalz durch die Nieren, *Verhandl d deutsch Gesellsch* **33** 409, 1921.

28 The preparation used was Para-thor-mone supplied by Eli Lilly and Company through the courtesy of Dr. J. H. Warvel.

units of the hormone were usually sufficient to increase the amount of circulating calcium in the blood, the maximum effect being manifested in from eight to twelve hours after administration²⁹ Determinations of serum calcium were made by the Clark-Collip modification of the method of Kramer and Tisdall³⁰ Determinations of plasma calcium were made by the same method, powdered heparin being used as an anticoagulant

The inflammatory reaction was produced by the blister method, used by Petersen³¹ for the study of the permeability of the capillaries, with slight deviations from his suggested technic A cantharides plaster, 1 cm square (U S P X), was placed on the skin of the volar aspect of the forearm just below the elbow, at 6 a m, and was removed four hours later The interval of time between the removal of the plaster and the first suggestion of the formation of a blister was designated the blister time (B T) When sufficient serum had accumulated, it was withdrawn, and at the same time blood was taken from the vein The protein content of the blister serum and blood serum was determined by the refractometric method, and the Reiss tables were used for the calculations, the exudate scale for the fluid of the blister and the serum scale for the blood serum The ratio of blister serum protein to blood serum protein is termed, by Petersen, the permeability ratio (P R)

Estimations for blood calcium were made as stated, in several instances One series of observations for control was made as outlined At 6 p m of the same day, 20 units of parathyroid extract were injected intramuscularly, the same amount was administered at midnight, and the routine procedure and observations of the preceding day were repeated, the opposite forearm being used By this procedure, the normal inflammatory reaction is compared with that occurring at the height of the effect of calcium in the blood and presumably in the tissues

The affinity of the tissue colloids for water was determined by the test of McClure and Aldrich³² Two tenths of a cubic centimeter of physiologic solution of sodium chloride was injected intracutaneously at 8 a m on the volar aspect of the forearm, just below the elbow The time of disappearance of the wheal was noted Twenty units of parathyroid extract were then administered at 6 p m and again at midnight, and the test was repeated at 8 a m and at noon of the succeeding day

TYPES OF CASES

The observations of the inflammatory reaction were made on patients with chronic pulmonary tuberculosis, of varying extent and activity As Petersen³² has found abnormal degrees of the permeability of the

29 Gordon, B L, and Cantarow, Abraham The Use of Parathyroid Extract in Hemorrhage, *J A M A* **88** 1301 (April 23) 1927 Cantarow, Abraham, Caven, W R, and Gordon, B L Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, *Arch Int Med* **38** 509 (Oct) 1926 Cantarow, Abraham, Dodek, S M, and Gordon, B L Calcium Studies in Jaundice, *Arch Int Med* **40** 129 (Aug) 1927

30 Clark, E P, and Collip, J B A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, *J Biol Chem* **63**:461 (March) 1925

31 Petersen, W F, and Willis, D A Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch Int Med* **5** 663 (Nov) 1926

32 Petersen, W F The Permeability of the Skin Capillaries in Various Clinical Conditions, *Arch Int Med* **1** 27 (Jan) 1927

capillaries in such patients, our observations obviously cannot be compared with those made on normal persons. However, the results obtained in the same person on successive days at the same hour and under the same conditions should be fairly comparable, the interval of time being too brief for any appreciable change in the clinical condition.

The patients on whom the intracutaneous test with a physiologic solution of sodium chloride was performed were suffering from cardiac or renal disease, some with and some without demonstrable edema.

TABLE 1—Results of Blister Test in Thirty Patients with Pulmonary Tuberculosis

Case	Blister Time *		Group I (Far Advanced Tuberculosis)		Serum Protein †		Permeability Ratio		Serum Calcium ‡		Plasma Calcium ‡	
	1§ 2#		Blister Protein †		1 2		1 2		1 2		1 2	
	1§	2#	1	2	1	2	1	2	1	2	1	2
1	3 40	5 20	6 14	6 65	7 29	8 32	82 8	79 9	9 3	10 4	9 1	10 6
2	3 25	4 10	6 33	6 16	8 66	8 24	73 2	74 6	10 3	10 5		
3	3 10	5 20	5 63	5 22	7 45	8 04	75 5	64 9	9 7	11 2		
4	2 30	7 00	5 76	6 21	7 47	8 05	77 1	77 1	9 4	9 5	9 3	9 9
5	2 30	3 20	4 50	3 40	4 60	5 20	97 8	65 3	10 6	10 4		
6	3 30	3 75	5 04	6 39	6 60	7 47	76 3	85 5	9 7	9 9		
7	4 30	3 25	6 22	6 61	7 21	7 52	86 2	87 8	10 2	11 3	9 9	11 5
8	3 15	3 15	6 56	5 73	6 63	6 54	98 9	87 6	9 4	9 8	9 1	10 2
9	2 30	2 30	7 56	6 96	8 87	8 94	85 3	77 8	9 6	10 4		
10	2 25	5 20	5 92	6 33	8 06	8 12	73 5	77 9	9 5	10 3	9 2	10 2
11	2 35	3 55	5 45	6 27	7 56	8 34	72 0	75 1	10 6	10 6		
12	7 30	5 45	5 43	6 99	8 56	8 63	63 4	80 6	10 8	11 2		
13	4 15	5 25	6 67	6 01	9 25	8 78	72 1	68 5	11 0	11 2		
14	5 20	6 30	5 62	5 27	7 32	7 17	76 7	73 5	9 1	10 0		
15	3 15	4 20	6 39	5 78	8 14	7 79	78 2	74 1	9 3	9 8	9 4	10 3
16	2 10	4 35	7 14	5 37	8 31	7 45	85 9	72 0	9 9	10 3	9 6	10 4
17	4 30	2 30	5 92	5 93	7 94	7 95	74 6	75 2	10 3	10 8	10 1	10 7
Average	3 35	4 35	6 31	5 96	7 64	7 79	79 8	76 3	9 9	11 0	9 4	10 4
			Group II (Moderately Advanced Tuberculosis)									
18	2 25	2 30	8 54	8 03	10 79	9 56	79 2	83 1	10 4	10 9	10 0	10 8
19	4 35	2 30	6 98	6 29	8 45	7 74	90 8	81 3	10 8	11 2		
20	3 10	2 55	5 52	5 54	7 27	7 09	75 9	78 2	11 1	11 4		
21	3 30	4 35	6 40	6 17	9 69	7 76	66 1	79 5	9 7	9 9		
22	4 15	5 55	5 90	6 76	8 34	8 30	70 7	81 5	10 2	11 0	10 0	11 0
Average	3 35	3 40	6 67	6 56	8 91	8 11	76 5	80 7	10 4	10 8	10 0	10 9
			Group III (Inactive Tuberculosis)									
23	3 20	2 30	5 82	5 88	8 24	8 12	70 6	72 3	9 4	10 2		
24	3 30	8 30	7 18	7 05	9 99	8 03	71 9	87 7	9 9	9 7		
25	3 15	3 25	6 99	5 75	10 07	9 39	69 4	61 2	10 3	10 5	10 1	10 7
26	6 50	8 55	5 43	6 12	7 46	7 51	72 7	81 5	9 1	10 3	8 8	10 5
27	2 45	3 25	5 15	5 44	8 33	9 31	61 8	58 4	10 6	10 9		
28	3 20	4 35	5 38	6 33	8 82	7 34	60 9	86 2	10 2	11 1	10 0	11 2
29	2 30	2 30	6 59	7 37	8 85	8 22	81 6	89 6	19 8	10 4	9 8	10 6
30	3 55	3 10	7 17	7 18	9 27	8 78	77 3	81 7	10 5	11 2		
Average	3 40	4 35	6 20	6 39	8 88	8 34	70 7	77 3	9 9	10 5	9 7	10 7

* Blister time expressed in hours and minutes

† Protein values expressed in Grams per hundred cubic centimeters

‡ Calcium values expressed in milligrams per hundred cubic centimeters

§ Before administration of parathyroid extract

After administration of parathyroid extract

RESULTS OBTAINED

Blister Test—The patients were divided into three groups according to the extent and activity of the pulmonary lesions, since Petersen found that variations in the permeability of the capillaries were dependent on the degree and type of the tuberculous process. The detailed results are presented in table 1.

Blister Time—In the group of seventeen patients with far advanced active pulmonary tuberculosis, the blister time varied from two hours and ten minutes to seven hours and thirty minutes, the average being three hours and thirty-five

minutes After the administration of parathyroid extract, the variation of time was from two hours and thirty minutes to seven hours, with an average of four hours and thirty-five minutes In twelve patients, the blister time was prolonged, in two it remained constant, and in three it was diminished

In the group of five patients with moderately advanced lesions, the time of appearance of the blister ranged from two hours and twenty-five minutes to four hours and thirty-five minutes, the average being three hours and thirty-five minutes After the administration of parathyroid extract, the time varied between two hours and thirty minutes and five hours and fifty-five minutes, with an average of three hours and forty minutes In three instances, the blister time was prolonged, and in two it was lessened

In the eight patients with slight, inactive lesions, the blister time varied from two hours and thirty minutes to six hours and fifty minutes, averaging three hours and forty minutes, after the injection of parathyroid extract, the time ranged between two hours and thirty minutes and eight hours and fifty-five minutes, averaging four hours and thirty-five minutes In five patients, the time was increased, in one it remained unchanged, and in two it was decreased

Blister Proteins—In group 1, there was one patient (case 5) with a marked secondary anemia and edema, and an extremely low serum protein content, in this case, the concentration of blister protein was 4.5 per cent before and 3.4 per cent after the administration of parathyroid extract

If this case is excluded, concentration of blister protein in this group ranged between 5.04 and 7.56 per cent, the average being 6.31 per cent, after the injection of parathyroid extract, it varied from 5.22 to 6.99 per cent, and averaged 5.96 per cent The concentration of protein was increased in eight cases and decreased in nine

In group 2, the concentration of blister protein varied between 5.52 and 8.54 per cent averaging 6.67 per cent, after the administration of parathyroid extract, the variation was from 6.17 to 8.03 per cent, with an average of 6.56 per cent The concentration was increased in two cases and decreased in three cases

In group 3, the blister protein content varied from 5.15 to 7.18 per cent and averaged 6.2 per cent, after the administration of parathyroid extract, the variation was from 5.44 to 7.37 per cent, with an average of 6.39 per cent The concentration was increased in six cases and decreased in two cases

Serum Protein—If case 5 in group 1 is excluded, the variation in the concentration of blood serum protein was between 6.6 and 9.25 per cent, the average being 7.64 per cent, after the administration of parathyroid extract, the concentration varied from 6.54 to 8.94 per cent and averaged 7.79 per cent It was increased in eleven cases and diminished in six

In group 2, the concentration ranged from 7.27 to 10.79 per cent, and averaged 8.91 per cent, after the administration of parathyroid extract it varied from 7.09 to 9.66 per cent, with an average of 8.11 per cent The concentration was decreased in all five patients

In group 3, the serum protein content ranged from 7.46 to 10.07 per cent, the average being 8.88 per cent, after the administration of parathyroid extract, the variation was between 7.34 and 9.39 per cent, averaging 8.34 per cent An increased concentration occurred in three cases and a decrease in five cases

Permeability Ratio—The ratio of the concentration of blister protein to that of serum protein in group 1 varied from 63.4 to 97.8 per cent, the average being 79.8 per cent, after the administration of parathyroid extract, it varied from 64.9 to 87.8 per cent, averaging 76.3 per cent It was increased in eight instances, stationary in one, and decreased in eight

In group 2, the permeability ratio ranged from 66.1 to 90.8 per cent, averaging 76.5 per cent, after the administration of parathyroid extract, it varied from 78.2 to 83.1 per cent with an average of 80.7 per cent. It was increased in four cases and decreased in one case.

In group 3, the variation was between 60.9 and 81.6 per cent, and averaging 70.7 per cent, after the administration of parathyroid extract it ranged from 58.4 to 89.6 per cent, the average being 77.3 per cent. The ratio was increased in six patients and decreased in two.

Serum and Plasma Calcium—The observations for calcium revealed nothing of unusual interest, except that the concentration of plasma calcium, which was slightly lower than that of serum calcium in most patients, after the administration of parathyroid extract was usually higher. The values for serum calcium were not appreciably increased in all cases, but, as shown by Hunter and Aub,³³ an increased availability and excretion of calcium may occur without a rise in blood calcium following the administration of parathyroid extract.

DISCUSSION OF RESULTS OF BLISTER TEST

If the time of appearance of the blister is an indication of the reaction of the tissues to irritation, it may be considered that in twenty of the thirty cases the rapidity of response to irritation was decreased after the administration of parathyroid extract, in three it was unchanged, and in seven it was increased. This would seem to support the conclusion that calcium tends to exert an inhibitory action on the production of inflammatory edema.

If, on the other hand, it is assumed that the permeability ratio, which is more or less directly dependent on the concentration of blister protein, is an index of the permeability of the capillaries, and, indirectly, of the inflammatory reaction, the results obtained are contradictory. The concentration of blister protein was increased in sixteen patients of this series and was decreased in fourteen, apparently indicating that the permeability of the capillaries in more than half of the cases was increased during the period of the increase in available tissue calcium. However, it is possible that the concentration of protein in the blister fluid may be dependent on factors other than the permeability to protein of the walls of the capillaries. Chief among these, perhaps, is their permeability to water and to crystalloids.

It is not unlikely that the concentration of blister protein depends on two variable factors—the amount of protein and the amount of water. If the former remains constant and the latter is diminished, the result will be an increased concentration of protein. Likewise, if both are diminished, but the water content is decreased relatively more than the protein, the same result will be obtained. A reduction in the amount of water in the blister may result from a diminution in the permeability

33 Hunter, D., and Aub, J. C. Lead Studies 15. The Effect of Parathyroid Hormone upon the Excretion of Lead and of Calcium in Patients Suffering from Lead Poisoning, *Quart J Med* 20 136 (Jan) 1927.

of the wall of the capillary to water or to crystalloids, the latter factor operating through the forces of osmosis. Furthermore, the inhibition of the inflammatory reaction by the excess of calcium may cause a diminution in the products of tissue disintegration accompanying the process; as a result of the subsequent relative reduction in osmotic pressure, less fluid will transude, although the amount of protein may be affected slightly.

It seems in these studies that the permeability ratio and the concentration of blister protein may not be true indexes of the permeability of the capillaries. There is one observation, however, which, though not of a definitely quantitative nature, may be considered significant. It was noted that after the administration of parathyroid extract, although the blister time may not have been prolonged or the concentration of protein decreased, the accumulation of fluid in the blister took place less rapidly than in the control test. In several instances, particularly in group 3, several hours elapsed after the first appearance of the inflammatory reaction before sufficient fluid had accumulated for determination of the protein content. This would seem to support the opinion that the increased concentration of protein is not due to an increase in the permeability of the capillaries but rather to a decreased transudation of water. It is not unlikely that the permeability to proteins is also diminished, but to a lesser degree, in the patients who show an increased concentration of blister protein after the administration of parathyroid extract. When the response in different persons is compared, the possibility of certain variable factors, such as the distribution of the capillaries circulation and the texture of the skin, should be recognized. This is true also of various transient physiologic and chemical changes which may occur in the same person. The data, therefore, should be considered critically.

INTRADERMAL TEST WITH PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE

Observations were made on twenty patients, as described before, suffering with cardiac or renal disease. The observations are detailed in table 2.

In eighteen patients, the level of the serum calcium ranged from 9.1 to 10.2 mg per hundred cubic centimeters, and the plasma calcium from 8.8 to 9.9 mg per hundred cubic centimeters. In cases 10 and 15 the patients had far advanced cardio-renal disease with general anasarca, the serum calcium values being 8.4 and 8.5 mg per hundred cubic centimeters, and the plasma calcium values, 7.9 and 8.3 mg per hundred cubic centimeters, respectively. In every instance the level of the blood calcium was raised following the administration of parathyroid extract.

The duration of the wheal corresponded fairly closely to the degree of edema present. The time varied from twenty-five (case 15) to eighty minutes. In seven cases, the injected fluid disappeared in less than sixty minutes, the low limit of normal, and in these patients there was definitely palpable edema. In three cases in which the disappearance time was sixty minutes, there was slight edema of the ankles.

In every instance, twelve hours after the second administration of parathyroid extract, there was a prolongation of the disappearance time of the injected fluid, varying from five to forty minutes and averaging twenty-four and one-half minutes. The results were particularly striking in that in all but one case the duration of the wheal was well above

TABLE 2—Results of Intracutaneous Test with Physiologic Solution of Sodium Chloride before, and Eight and Twelve Hours after the Administration of Parathyroid Extract in Twenty Patients with Cardiovascular Renal Disease

Case	Edema	Control			Eight Hours			Twelve Hours		
		Min-utes	Calcium *		Min-utes	Calcium *		Min-utes	Calcium *	
			Serum	Plasma		Serum	Plasma		Serum	Plasma
1	None	65	10.2	9.8	80			85		
2	Slight, ankles	60	9.8	9.5	65			85		
3	Slight	55	9.2	8.9	65			80		
4	None	70	9.7	9.3	70			85		
5	None	75	9.1	8.8	90	11.1	10.8	110	10.3	10.6
6	Ankles	60	10.2	9.9	75	12	12.2	65	11	10.8
7	None	70	10	9.5	80	12.2	11.9	100	11.1	11.4
8	None	65	9.3	9.1	80	12	12.1	80	10	10.2
9	None	80	10.1	9.9	85	12.3	12.5	105	11.2	11.5
10	Legs, face, ascites	45	8.4	7.9				70	10.1	10.4
11	None	75	9.6	9.2				95		
12	Ankles, legs	55	9.7	9.3				80		
13	Slight, ankles	60	9.4	8.8				80		
14	Legs, ascites	50						85		
15	General anasarca	25	8.5	8.3				40	9.2	9
16	None	65						90		
17	Ankles	55						85		
18	Legs	50						80		
19	None	60						100		
20	None	70						105		

* Calcium values are expressed in milligrams per hundred cubic centimeters

the normal low limit, and in eleven it was above the high limit. In the single case in which the time remained below normal (case 15), it was increased from twenty-five to forty minutes. This patient was the only one of the series with demonstrable edema of the arms, the test being performed, therefore, in definitely edematous tissues.

In nine patients, the test was also performed eight hours following the injection of parathyroid extract (table 2). The disappearance time was found to be increased in all but one (case 4), the prolongation in the other eight cases varying from five to fifteen minutes and averaging eleven minutes. Determinations made eight and twelve hours after the administration of parathyroid extract showed that the serum and plasma calcium were higher at the end of eight hours than after twelve hours. In every case but two (cases 6 and 8), the disappearance time was

distinctly longer after twelve hours than after eight hours. This serves to support the hypothesis stated previously, that the production of a calcium effect is dependent not entirely on an elevation of total circulating calcium, but on an increase in the availability of calcium. This may be expressed as an increase in the ratio of the diffusible or the ionized fractions to the total calcium.

In this group of patients, the edema was of the noninflammatory type. It would appear that as a result of the increase in available calcium following the administration of parathyroid extract, the capacity of hydration of the tissue colloids was diminished.

Some time after this work had been completed, McCann³⁴ reported three cases of nephritis with edema in which he had used parathyroid extract in therapeutic dosage. Marked and prolonged diuresis occurred in each case, with diminution in the edema and increased urinary excretion of sodium chloride. These observations seem to coincide with the results of the intradermal test with physiologic solution of sodium chloride, mentioned previously.

CONCLUSIONS

It appears that if the blister test is to be used to study the permeability of the walls of the capillaries, perhaps more reliance should be placed on the blister time and the rate of accumulation of fluid in the blister than on the concentration of protein in the blister fluid or the permeability ratio.

Utilizing the blister test as a means of studying inflammatory edema, it would appear that an increase in available circulating calcium effected by the administration of parathyroid extract exerts a slight but rather constant and definite inhibitory effect on the inflammatory process. This effect may be due to a decrease in the permeability of the capillaries or to a relatively decreased osmotic pressure in the irritated tissues. If the action is chiefly one of diminished permeability, the passage of water through the walls of the capillaries is inhibited in many cases to a greater degree than is the passage of proteins. It is possible that the result is due to a combined effect on osmosis and permeability.

The observations of the intradermal test with physiologic solution of sodium chloride suggest that calcium decreases the affinity of the tissue colloids for water. The exact mode of action is not entirely clear. It is not unlikely that the calcium replaces the sodium which has accumulated in the tissues, the reduction in edema being due to the fact, as mentioned by Fischer,⁶ that calcium protein compounds have a lower capacity for hydration than have sodium protein compounds.

³⁴ McCann, W. S. Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, *J. A. M. A.* **90** 249 (Jan 28) 1928.

SUMMARY

1 The principal factor underlying the production of inflammatory edema is probably increased permeability of the walls of the capillaries. It appears that the administration of calcium exerts an inhibitory influence in this type of edema perhaps as the result of the diminution in the permeability of the capillaries.

2 The chief factor underlying the development of noninflammatory edema is probably an increased capacity of the tissue colloids for hydration. Retention of sodium is an important factor, but whether primary or secondary, is uncertain.

3 Inflammatory edema was studied by the blister method, the observations being repeated at the height of the effect of calcium produced by the intramuscular administration of parathyroid extract.

4 The increase of calcium seemed to have a slight but definite inhibitory effect on inflammatory edema.

5 The affinity of the tissue colloids for water was studied by the intradermal injection of physiologic solution of sodium chloride, the test of McClure and Aldrich, in a group of twenty patients with cardiac or renal disease, some with and some without edema. The test, repeated after the administration of parathyroid extract, indicated a marked decrease in the capacity of the tissues for hydration, which accompanied the increase in available circulating calcium.

Book Reviews

SINDROMI NEURO-IPOFISARIE By G DI GUGLIELMO Price, 50 Lire Pp 311
Milano S A Istituto editoriale scientifico, 1928

In the introduction the author recalls the history of our conceptions concerning the relationship of the pituitary gland to the hypothalamus since Marie's description of acromegaly, noting the emphasis on the hypophysis, following Froehlich, the reaction led by Camus and Roussy, and finally the conception of Perde that there is a symbiotic collaboration of neurohypophysis and hypothalamus. It should be noted from the outset that the author, although professing to treat of syndromes due to lesions of the pars posterior hypothalamus, inserts also many conditions due purely to lesions of the anterior lobe, such as the malady of Simmonds.

The first chapter is concerned with anatomy. The description of the hypothalamus follows Ramirez-Corria (reference not given), le Grand and Kary. The author seems not to be familiar with the fundamental work of Spiegel and Zweig and of Greving, not to mention the work of Malone in this country. His description of the hypophysis occupies only half a page. The chapter closes with an account of the tractus supraoptico-hypophysis.

The second chapter dealing with the physiology and physiopathology is more adequate and gives a fairly complete summary of experimental work on the relationship of pars posterior and hypothalamus to such functions as regulation of the metabolism of salt, water, carbohydrates, and fat, growth, sexual activity, sleep and heat production. He concludes that anatomic connections and functional correlations exist between the hypothalamus and pars nervosa in such manner that they constitute a unitary system, each one influencing the other, the pars nervosa exercising its influence by its secretion and the hypothalamus by nervous impulses. Disturbances due to lesions of this system he proposes to call neurohypophysial syndromes.

In the etiology of these syndromes, tumors occupy a prominent place and the author lists adenomas, sarcomas, gliomas, fibromas, keratomas, carcinomas and hypophyseal duct tumors. In this list he follows the older pathologists, since carcinomas, fibromas and gliomas are rare and sarcomas are never found in the hypophysis. Other causes listed are hemorrhage, thrombosis, embolism, cysts, trauma and foreign bodies.

The author essays a classification of neurohypophysial syndromes as follows:

- 1 Syndromes due to altered metabolism of fat
 - a Defect syndromes (malady of Simmonds)
 - b Excess syndrome (obesity, adiposogenital dystrophy)
 - c Mixed syndromes (progressive lipodystrophy)
- 2 Syndromes due to altered water-salt metabolism
 - a Defect syndromes (oliguria)
 - b Excess syndromes (polyuria, diabetes insipidus)
- 3 Syndromes due to altered growth
 - a Defect syndromes (nanism, infantilism)
 - b Excess syndromes (gigantism, acromegaly, pubertas praecox)
- 4 Syndromes due to altered carbohydrate metabolism
 - a Diabetes mellitus (atypical forms)

This classification is misleading, for obesity and adiposogenital dystrophy are deficiency syndromes, and the opposite of the malady of Simmonds is to be sought in acromegaly, just as gigantism is the opposite of infantilism. Most writers would consider the obesity to be the opposite of diabetes mellitus. Moreover, the malady of Simmonds, nanism, gigantism and acromegaly do not pertain to the neurohypophysis-hypothalamic system but rather to the pars anterior.

The author points out that the diagnosis of these syndromes is aided considerably by ocular defects and radiography. He is opposed to surgical treatment, more favorably inclined toward cautious radiotherapy and believes in the efficacy of extracts of the anterior lobe which have been shown experimentally to be totally inactive.

The second part of the monograph deals with the deficient syndromes of his classification, each being considered separately with clinical examples. He begins with Simmond's disease, which he defines as a morbid entity characterized clinically by denutrition, adynamia, apathy, somnolence, precocious senility, falling of hair and teeth, dryness of skin, amenorrhea, atrophy of internal and external genitalia, low blood pressure, eosinophilia and microsplachnia, and anatomically by atrophy of the anterior lobe of the hypophysis from various causes, with probably participation of certain diencephalic centers. The history, symptoms, course, diagnosis, pathologic anatomy, etiology, pathogenesis, prognosis and therapy are discussed. The constant efficacy of the anterior lobe in the treatment is emphasized, which is interesting when one considers that such preparations are totally inactive in experimental animals. A clinical case is given with a complicated syndrome including diabetes insipidus. The patient was a prostitute, aged 29, syphilitic, who seems to have improved remarkably following the administration of pituitary gland.

Adiposogenital dystrophy is treated in the same way with three cases as illustrations: the first a tumor of the hypophysis, the second too briefly recorded to allow of a diagnosis and the third probably a tumor of Rathke's pouch. All are clinical cases without verification at necropsy or operation.

In the section dealing with progressive lipodystrophy the author has great difficulty in bringing the neurohypophysial system into its etiology. This section is also illustrated by a clinical case.

The discussion of diabetes insipidus is more adequate, as the author is here on firmer ground. He seems on the whole inclined to accept the conclusions of Zadek that destruction of the hypothalamus is responsible for the reduction in power of the tissues to fix water, while the pars intermedia and peduncle of the hypophysis are responsible for hypochloremic diabetes insipidus. He does not make any attempt to reconcile these conclusions with the fact that experimental removal of the pars intermedia and pars nervosa does not result in polyuria. Seven cases of diabetes insipidus are discussed. Necropsies were obtained in two of them, in the second of these the patient had also a marked glycosuria. In the first case, examination of the hypophysis showed the presence of atypical cells in the anterior lobe, of basophil cells in the posterior lobe and of an unusual amount of colloid in the neurohypophysis. Nothing is said of the hypothalamus. In the second case, examination of the hypophysis showed a considerable area of the anterior lobe to be transformed into connective tissue and thickening of the capsule. The pancreas is said to have been normal. Again nothing is said of an examination of the hypothalamus.

The monograph closes with a chapter on syndromes of altered somatic development, although the author states that these cases are not due to lesions of the neurohypophysial system. A clinical case of macrogenitosomia praecox is given without evidence of involvement of the hypophysial region. After discussing the different classifications proposed for these developmental disorders three cases of hypophysial dysgenopathy are discussed, two with necropsy. In the first case there is no clinical history. The necropsy disclosed a congenitally defective heart. In the report of the necropsy is the bare statement that the "infantilism was very manifest." In the anterior lobe of the hypophysis a large cyst was found, and there was marked hyperemia of the remaining glandular tissue. The second observation concerns a man, aged 19, with endocarditis causing mitral, tricuspid and aortic insufficiency. In infancy he had had a febrile disorder which resulted in a deformity of the right foot. He was underdeveloped. Examination of the hypophysis revealed a large cyst between the anterior and the posterior lobes.

The monograph as a whole adds nothing to our knowledge of the pathophysiology of either the hypophysis or the hypothalamus.

BLOOD AND URINE CHEMISTRY By R B H GRADWOHL and IDA E GRADWOHL
St Louis C V Mosby Company, 1928

The first twenty chapters of this volume consist of a clear, concise and thorough description of the methods ordinarily used in the chemical analysis of blood and urine with special emphasis laid on colorimetric procedures. It is to be regretted that mention is not made of the technic of estimations of sodium or potassium in the blood or of total bases, of blood hemoglobin, blood sulphates and fractional determination of plasma proteins. The only method testing chlorides in the plasma is the Volhard-Arnold method, and none of the recent p_H methods are even mentioned. Throughout the book there are lengthy quotations from articles in the literature, giving the appearance of an exhaustive review but, unfortunately, they are not always up-to-date, although in some places they are. For example, in the discussion of the dextrose threshold and dextrose tolerance test, mention is not made of the vast amount of careful work in Faber's clinic, and in the chapter on nephritis there is nothing quoted more recent than 1917 or 1918, except in the discussion of the toxemias of pregnancy.

The arrangement is sometimes puzzling. For example, the whole subject of blood calcium and a long review of the chemical changes in the blood in intestinal obstruction are given in the chapter on nephritis, whereas nephrosis is briefly mentioned. The chapters in which gout and renal glycosuria are discussed are much better.

The last part of the book consists of a review of basal metabolism most of which is quoted partly from McLeod's book on physiology and biochemistry in modern medicine, Boothby and Sandeford's laboratory manual on basal metabolism and the booklet of description of technic which comes with the Benedict-Roth apparatus.

The book is well printed and excellently illustrated. It is to be hoped that the second edition will be a little more even in its subject matter and up-to-dateness.

OPERATIVE SURGERY By J SHELTON HORSLEY Third edition Price, \$15
St Louis C V Mosby Company, 1928

Since the last edition in 1924, much material has been added to this book, one of the standard works on operative surgery, so that it now embraces nearly 900 pages. It is well illustrated with drawings, mostly original, and is beautifully printed and bound.

The new material deals especially with the heart and lungs, as well as with several new intracranial operations, and makes up an admirable summary of the advances in surgery during the past few years.

While matters of diagnosis and nonsurgical aspects of disease are of course excluded, the work contains summaries of many of the newer contributions to the basic sciences underlying our surgery, such as the work of Gye, Barnard, and Bell on carcinoma, and a great deal of modern experimental surgery is summarized in the proper places when it has bearing on clinical problems.

The text is clear, and by frequent reference to the illustrations a good idea may be gained of the technic of each particular operation. The choice of material has been on the whole wisely made, the commoner operations receiving the most attention. Bone surgery is perhaps somewhat slighted in view of the increasing specialism of this sort of work and the many volumes by other authors devoted to it.

I would say that the only criticism to make is the undue amount of space of nearly 100 pages given to the discussion of blood vessel surgery, including transfusions of blood. In the latter field especially, many of the statements regarding the advantages of the various methods might well be argued. Certainly, Crile's method of direct vascular anastomosis is rarely carried out today.

On the whole, the reviewer feels convinced that this work is the most valuable treatise on the subject today.

PHARMACOTHERAPEUTICS, MATERIA MEDICA AND DRUG ACTION By S SOLIS-COHEN and T S GITHENS Price, \$15 Pp 2009 New York D Appleton & Company, 1928

This work is a noteworthy addition to the available texts on therapeutics and pharmacology, being the most comprehensive and complete work on drug therapeutics in the English language. The authors present pharmacologic justification for the use of the drugs used in modern therapeutics. Pharmacology is well covered, and in many respects this text may even be considered as a textbook of pharmacology, though it is written from the clinical standpoint using pharmacology as a basis for therapeutic uses. In some respects, the authors are conservative, whereas in others they are apparently overoptimistic in that some of their conclusions are drawn from evidences which could scarcely be considered as adequate.

The book is exceedingly valuable and can be read with profit by both the clinician and the laboratory man. To the research man the book is both valuable and disappointing since authors' names are generously cited, but literary references are not given.

THE TREATMENT OF DIABETES MELLITUS By ELLIOTT P JOSLIN Fourth edition Price, \$9 Pp 998 Philadelphia Lea & Febiger, 1928

In 1916, the first edition of Joslin's "Diabetes" appeared in a large volume of 440 pages. The new fourth edition, arriving just twelve years later, contains 998 pages. Such are the complications of modern medicine that one student working intensively at one disease can produce such an encyclopedic volume. The work represents the characteristic Joslin trait of painstaking study of his own work and of careful inquiry into the work of others, all with one end in view—improvement in the treatment of the diabetic patient. The reviewer finds it difficult to attempt a detailed comment, the book contains so much that one can open it at random and receive almost at a glance an impetus to review his own cases of diabetes. This volume is so full of information on so many aspects of the disease other than treatment that it is today the outstanding practical treatise on diabetes mellitus.

LOBAR PNEUMONIA By L R SANTE Price, \$3 New York Paul B Hoeber, 1928

Sante's brief monograph records his experience in the x-ray examination of patients with lobar pneumonia at the St. Louis City Hospitals and elsewhere in St. Louis.

A reader not conversant with the technical difficulties of irradiation of patients with pneumonia and the bewildering clinical problem of differential diagnosis of x-ray films of the chest in pneumonia would find in this book little to suggest such difficulties.

Few clinical workers will deny the immense value of the roentgen ray in establishing an essentially normal condition of the lung when disease is feared or in outlining roughly the anatomic distribution of lesions when lesions exist, however, the time has not yet arrived when unsupported x-ray evidence will always answer the question, "Is it consolidation or is it fluid?"

INDEX TO VOLUME 42

	PAGE		PAGE
Acromegaly, roentgen ray therapy of hypophysis in patient with	703	Blood, behaviour of plasma chlorides in obstructive jaundice	491
Agatston, S A Changes in fundus oculi as definite index to arterial disease	455	chemical analyses of, in patients having senile cataract	376
Agranulocytosis (Schultz) and the agranulocytic complex	893	pressure, arterial hypertension and physical work	297
Albuminuria, lordosis as cause of postural	440	pressure, electrocardiogram in hypertension	512
Alkalosis, in patients with peptic ulcer	79	pressure, experimental hypotension in rabbits	56
Allan, W Inheritance of migraine	590	pressure, presenile disturbances of	379
Allen, R E Roentgen ray therapy of hypophysis in patient with acromegaly, its effect on dextrose tolerance	703	sugar, distribution of, between corpuscles and plasma in diabetic and in alimentary hyperglycemia	931
Allergy, allergic hypothesis and bacteriology of rheumatic fever	301	value of the Drazo test on	386
atopy, blood calcium and gastric analysis	865	Bockus, H L Simultaneous nonsurgical drainage of gallbladder and intravenous cholecystography	735
skin sensitivity of rheumatic subjects to streptococcus filtrates	784	Body surface, area of, and measurements of normal heart	135
Altshuler, A M Gastric secretion, its alteration by use of atropine, epinephrine and pilocarpine	117	Book Reviews	
Andrews, E New clinical test for tissue thirst	776	Blood and Urine Chemistry, R B H Gradwohl and I E Gradwohl	955
Anemia, palm color test, method for diagnosis of plethora and	533	Constitutional inadequacies An introduction to the Study of Abnormal Constitutions, N Pende	798
pernicious, edema and reduction in excretion of water	425	Dental Infection and Systemic Disease, R L Haden	454
serums from normal and anemic persons, effect of, on growth of seedlings	909	Diabetic Manual for Patients, H J John	610
tapeworm	313	Hormone und Innere Sekretion, F Laquer	608
Arquin, S Relation of reaction to epinephrine to potassium calcium ratio and other ratios	256	Klinische Gasstoffwechseltechnik, H W Knipping and H L Kowitz	150
Arteries, changes in fundus oculi as definite index to arterial disease	455	Krankheitslehre der gegenwart Strömungen und Forschungen in der Pathologie seit 1914 Weissenschaftliche Forschungsberichte Naturwiss Reihe, Band XVII, G Herxheimer	610
coronary, disease of, occurrence without gross cardiac hypertrophy	74	Lobar Pneumonia, L R Sante	956
Arthritis, chronic, synovial fluid in	675	Local Immunization, A Besredka, Translated by H Plotz	454
Artichokes, Jerusalem, utilization in diabetes	64	Low Blood Pressure Its Cause and Significance, J F Halls Dally	800
Asthma, bronchial, peptone treatment in	368	Modern Medical Monographs, H Maclean	148
Atopy See Allergy		Operative Surgery, J S Horsley	955
Atropine, alteration of gastric secretion by use of	117	Pathological Physiology of Internal Diseases Functional Pathology, A W Hewlett Revised in memoriam by his colleagues With 164 illustrations	453
Bach, C T Experimental hypotension in rabbits	56	Pharmacotherapeutics, Materia Medica and Drug Action, S Solis Cohen and T S Githens	956
Bacillus, mucosus capsulatus, septicemia due to strain of, in case of diabetes mellitus	331	Practical Gastrosocopy, J Rachet	454
Bairath, E Arterial hypertension and physical work	297	Questions Physiologiques D'Actualite, L Binet	150
Presenile disturbances of blood pressure	379	Sindromi neuro ipofisarie, G di Guglielmo	953
Barker, M H Cardiozol, some experimental effects of this drug on cardiorespiratory mechanism	14		
Beattie, W W Septicemia due to strain of bacillus mucosus capsulatus group in case of diabetes mellitus	331		
Bloedorn, W A Danger of administration of ephedrine in heart failure	322		

INDEX TO VOLUME 42

Book Reviews—Continued	PAGE	PAGE	
Syphilis und innere Medizin, III Die Syphilis des Zirkulations und Respiration Traktes und der Innersekretorischen Drüsen Syphilis und Blutkrankheiten, H Schlesinger	453	Christian, H A Relapsing febrile nodular nonsuppurative panniculitis 338	
The Brain from Ape to Man A Contribution to the Study of the Evolution and Development of the Human Brain, F Tilney	799	Connor, C L Generalized granulomatous lymphadenitis associated with diffuse progressive fibrosis of lungs 822	
The International Medical Annual	610	Cooksey, W B Thyroid disease, an experimental study 1	
The Mechanics of the Digestive Tract, W C Alvarez	609	Creatin, ingested, its utilization and rate of excretion by arthritic and normal subjects 901	
The Medical Department of the United States Army in the World War Training Volume 7	609	Criep, L H Atopy, blood calcium and gastric analysis 865	
The Medical Department of the United States Army, Volume 12 Part 1, Physical Reconstruction and Vocational Education Part 2, The Army Nurse Corps	609	Curtis, A C Production of renal injury in white rat by protein of diet, dependence of injury on duration of feeding, the amount of protein and kind of protein 801	
The New York Academy of Medicine Lectures on Medicine and Surgery First Series	608	Davidson, A Absorption of undigested proteins in human beings, the absorption of unaltered egg protein in adults 409	
The Significance of the Physical Constitution in Mental Disease, F I Wertheimer	149	Dextrose, tolerance, comparison of effects of general diets and of standardized diets on 872	
The Simple Goitre, R McCarrison	607	tolerance, roentgen ray therapy of hypophysis in patient with acromegaly, its effect on 703	
The Treatment of Diabetes Mellitus, E P Joslin	956	tolerance test, its use in determination of severity of diabetes mellitus 443	
Traite de Physiologie, Normale et Pathologique, G H Rogers	609	Diabetes insipidus, in xanthomatosis and the reticulo endothelial system 611	
Tratado de la Diabetes, P Escudero	607	mellitus, pancreatic activity in 560	
Ueber Erveisbeschränkung in der Behandlung des Diabetes Gravis, K Peten	610	mellitus, septicemia due to strain of bacillus mucosus capsulatus group in case of 331	
Bourne, W Effects of morphine and ether on function of kidneys	248	mellitus, statistical study of 2,000 cases 217	
Bram, I Tolerance for quinine in exophthalmic goiter	53	mellitus, use of dextrose tolerance test in determination of severity of 443	
Bronchomoniliasis, report of case from Porto Rico	500	mellitus, utilization of Jerusalem artichokes by patient with 64	
Brunner, M Absorption of undigested proteins in human beings, absorption of unaltered fish proteins in adults	172	Diarrhea, pancreatogenous fatty 352	
Buchbinder, W C Experimental obstructive jaundice, age factor in production of bradycardia	743	Diazo Reaction, value of, on blood 386	
Cajori, F A Ingested creatine, its utilization and rate of excretion by arthritic and normal subjects	901	Dickens, P F Danger of administration of ephedrine in heart failure 322	
Calcinosis, scleroderma and	467	Diet, comparison of effects of general diets and of standardized diets on tolerance for dextrose 872	
Cantrow, A Effect of parathyroid extract on certain factors underlying the production of edema	939	protein, production of renal injury in white rat by 801	
Cardiozol, experimental effects on cardiorespiratory mechanism	14	Diphtheria, electrocardiogram in 23	
Carpenter, T M Utilization of Jerusalem artichokes by patient with diabetes	64	Duke, W W Palm color test, simple practical clinical method for diagnosis of anemia and plethora 533	
Cataract, senile, chemical analyses of blood in patients having	376	Durham, R H Scleroderma and calcinosis 467	
Chloride, total concentration and acidity of gastric contents	106	Dyas, F G Syphilis of stomach, with special reference to certain diagnostic criteria 718	
Cholecystography, intravenous, simultaneous nonsurgical drainage of gallbladder and	735	Edema, and reduction in excretion of water in pernicious anemia 425	
		effect of parathyroid extract on certain factors underlying production of 939	
		Electrocardiogram, hypertension and in diphtheria 512	
			23

INDEX TO VOLUME 42

	PAGE		PAGE
Emotions, gastro intestinal reaction to the	282	Hanzlik, P J Continued administration of iodide and other salts, comparative effects on weight and growth of the body	579
Encephalitis, epidemic	151	Heart, age factor in production of bradycardia in experimental obstructive jaundice	743
Enteritis See Gastro Intestinal Tract		area of body surface and measurements of normal heart	135
Ephedrine, in heart failure, danger of administration	322	circulation, review of technical methods of demonstrating, modification of colloid and corrosion technique	846
Epinephrine, alteration of gastric secretion by use of	117	danger of administration of ephedrine in heart failure	322
relation of reaction to potassium calcium ration and other ratios	256	Henner, K Epidemic encephalitis, as observed at the first Czech Medical Clinic in Prague	151
Esophagus, ulceration of	521	Horiuchi, K Pancreatic function, pancreatic activity in diabetes mellitus	560
Ether, effects of, on kidney function	248	Hueper, W C Agranulocytosis (Schultz) and the agranulocytic complex	893
Ewing, P Effect of administration of medicinal iron on iron reserve, an experimental study	600	Huffman, M Total chloride concentration and acidity of gastric contents, a comparative study	106
Exophthalmos, in xanthomatosis and the reticulo endothelial system	611	Hyperglycemia See Blood, sugar	
Eye, changes in fundus oculi as definite index to arterial disease	455	Hypertension See Blood, pressure	
Feldman, M Ulceration of esophagus, experimental study	521	Hypertrophy, cardiac, disease of coronary arteries without gross	74
Forkner, C E Synovial fluid in chronic arthritis, bacteriology and cytology	675	Hypophysis See Pituitary Body	
Freilich, E B Lordosis as cause of postural albuminuria	440	Hypotension See Blood, pressure	
Friedenwald, J Ulceration of esophagus, experimental study	521	Imazu, T Pancreatic function, pancreatic activity in diabetes mellitus	560
Gaebler, O H Alkalosis in patients with peptic ulcer	79	Pancreatic function, quantitative estimation of pancreatic secretion	270
Galbreath, W R Bronchomoniliasis, report of case from Porto Rico	500	Immunity, production of active immunity against fatal outcome of experimental fecal peritonitis	415
Gallbladder, simultaneous nonsurgical drainage of, and intravenous cholecystography	735	Insulin, commercial, does it contain what hitherto has been called vitamin B?	766
Gastro Intestinal Tract, enteritis, uremia, experimental	835	Iodide, and other salts, continued administration of, comparative effects on weight and growth of body	579
reaction to emotions, role of the vegetative system	282	Iron, medicinal, effect of administration of, on iron reserve	600
Gatewood, W E Alkalosis in patients with peptic ulcer	79	Irvine Jones, E I M Skin sensitivity of rheumatic subjects to streptococcus filtrates, its relationship to rheumatic fever	784
Gershon Cohen, J Simultaneous non surgical drainage of gallbladder and intravenous cholecystography	735	Isaacs, R Effects of serums from normal and anemic persons on growth of seedlings	909
Gibson, E E Continued administration of iodide and other salts, comparative effects on weight and growth of body	579	Tapeworm anemia, therapeutic observations	313
Ginter, exophthalmic, tolerance for quinine in	53	Iversen, P Pernicious anemia, edema and reduction in excretion of water	425
Gold, H Prevention of experimental exudates by parathyroid hormone (Collip)	576	Jacobs, L Value of Diazo test on blood	386
Goldblatt, H Peritonitis, production of active immunity against fatal outcome of experimental fecal peritonitis	415	Jaundice, bile acids in	916
Gordon, B Effect of parathyroid extract on certain factors underlying production of edema	939	experimental obstructive, age factor in production of bradycardia	743
Gorham, F D Total chloride concentration and acidity of gastric contents, a comparative study	106	obstructive, behaviour of plasma chlorides in	491
Gustafson, F G Effects of serums from normal and anemic persons on growth of seedlings	909		

INDEX TO VOLUME 42

	PAGE		PAGE
John, H J Diabetes, statistical study of 2,000 cases	217	Menkin, V Relative lymphocytosis in hyperthyroidism	419
Johnstone, B I Toxicity of novasurol, its action on kidney of rabbit	189	Merbaphen See Novosural	
Katayama, I Bile acids in jaundice	916	Metabolism, basal, and thyroid gland	47
Keith, H M Toxicity of novasurol, its action on kidney of rabbit	189	Meulengracht, E Pernicious anemia, edema and reduction in excretion of water	425
Kerr, H D Some observations on scapulae of the Chinese	508	Migraine, inheritance of	590
Kidneys, effect of morphine and ether on function of	248	Miller, H R Disease of coronary arteries, occurrence without gross cardiac hypertrophy	74
production of renal injury in white rat by protein of diet	801	Mills, C A Functional insufficiency of suprarenal glands	390
urea tolerance test, an index of renal function	877	Morphine, effects of, on function of kidneys	248
King, J T Secretin not a hematopoietic stimulant	762	Morrison, M E Behaviour of plasma chlorides in obstructive jaundice	491
King S E Urea tolerance test, an index of renal function	877	Muntwyler, E Alkalosis in patients with peptic ulcer	79
Kissane, R W Area of body surface and measurements of normal heart, preliminary report	135	Myers, V C Alkalosis in patients with peptic ulcer	79
Kuramochi, K Pancreatic function, pancreatic activity in diabetes mellitus	560	Chemical analyses of blood in patients having senile cataract	376
Pancreatic function, quantitative estimation of pancreatic secretion	270	Nakazawa, F Pernicious anemia, edema and reduction in excretion of water	425
Levine, S A Cardiozol, some experimental effects of this drug on cardiorespiratory mechanism	14	Nathanson, M H The electrocardiogram in diphtheria	23
Levinson, S A Relation of reaction to epinephrine to potassium calcium ratio and other ratios	256	Newburgh, L H Production of renal injury in white rat by protein of diet, dependence of injury on duration of feeding the amount of protein and kind of protein	801
Lewison, M Lordosis as cause of postural albuminuria	440	Novasurol, toxicity of, action on kidney of rabbit	189
Lisser, H Roentgen ray therapy of hypophysis in patient with acromegaly, its effect on dextrose tolerance	703	O'Brien, C S Chemical analyses of blood in patients having senile cataract	376
Lobeline, alpha, as respiratory stimulant	180	Okada, S Pancreatic function, pancreatic activity in diabetes mellitus	560
Lordosis, as cause of postural albuminuria	440	Pancreatic function, quantitative estimation of pancreatic secretion	270
Lueders, C W Gastrointestinal reaction to the emotions, role of the vegetative system	282	Palm Color Test See Anemia	
Lungs, progressive fibrosis of, associated with generalized granulomatous lymphadenitis	822	Pancreas, pancreatic activity in diabetes mellitus	560
Lymphadenitis, generalized granulomatous, associated with diffuse progressive fibrosis of lungs	822	pancreatogenous fatty diarrhea	352
Lymphocytes, relative lymphocytosis in hyperthyroidism	419	quantitative estimation of pancreatic secretion	271
McCullagh, E P Parathyroid glands, their relationship to thyroid, with special reference to hyperthyroidism	546	Panniculitis, relapsing febrile nodular non suppurative	338
McElroy, W S Atopy, blood calcium and gastric analysis	865	Parathyroid, extract, effect of, on certain factors underlying the production of edema	939
Marshall, W R Alpha lobeline as a respiratory stimulant	180	glands, relationship to thyroid with special reference to hyperthyroidism	546
Mason, E H Septicemia due to strain of bacillus mucosus capsulatus group in case of diabetes mellitus	331	hormone (Collip), prevention of experimental exudates by the	576
		Peptic ulcer, alkalosis in patients with ulceration of esophagus, experimental	79
		Peptone, treatment, in bronchial asthma	368
		Peritonitis, production of active immunity against fatal outcome of experimental fecal	415

INDEX TO VOLUME 12

	PAGE	PAGE	PAGE
Peterson, W L Relation of reaction to epinephrine to potassium calcium ratio and other ratios	256	Shands, A R Synovial fluid in chronic arthritis, bacteriology and cytology	675
Pilocarpine, alteration of gastric secretion by use of	117	Singer, H A Syphilis of stomach, with special reference to certain diagnostic criteria	718
Pituitary Body, roentgen ray therapy of hypophysis in patient with acromegaly	703	Smith, J H Basal metabolism, influence of work with special reference to thyroid gland	47
Plethora, palm color test, method for diagnosis of anemia and	533	Smith, M Tapeworm anemia, therapeutic observations	313
Poston, M A Synovial fluid in chronic arthritis	675	Somogyi, M Distribution of blood sugar between corpuscles and plasma in diabetic and in alimentary hyperglycemia	931
Proteins, absorption of unaltered egg protein in adults	409	Squier, T L Experimental hypotension in rabbits	56
absorption of unaltered fish proteins in adults	172	Stehle, R L Effects of morphine and ether on function of kidneys	248
diet, production of renal injury in white rat by	801	Steinberg, B Peritonitis, production of active immunity against the fatal outcome of experimental fecal peritonitis	415
Quinine, tolerance, in exophthalmic goiter	53	Stilz, E Ingested creatin, its utilization and rate of excretion by arthritic and normal subjects	901
Ribson, S M Value of Diazo test on blood	386	Stomach, gastric secretion, its alteration by use of atropine, epinephrine and pilocarpine	117
Ragins, O B Lordosis as cause of postural albuminuria	440	syphilis of, with special reference to certain diagnostic criteria	718
Ramirez, M A Peptone treatment in bronchial asthma	368	total chloride concentration and acidity of gastric contents	106
Ravdin, I S Behaviour of plasma chlorides in obstructive jaundice	491	Streicher, M H Experimental uremia uremic enteritis	835
Respiration, alpha lobeline as respiratory stimulant	180	Streptococci, skin sensitivity of rheumatic subjects to streptococcus filtrates	784
effects of ergonovine on cardiorespiratory mechanism	14	Stroud, C M Total chloride concentration and acidity of gastric contents, a comparative study	106
Reticulo Endothelial System, xanthomatosis and the	611	Stucky, C J Does commercial insulin contain what has hitherto been called vitamin B?	780
Rheumatic fever, bacteriology of, and the allergic hypothesis	301	Sturgis, C C Tapeworm anemia, therapeutic observations	313
skin sensitivity of rheumatic subjects to streptococcus filtrates	784	Suprarenals, functional insufficiency of	390
Roentgen Rays, therapy, of hypophysis in patient with acromegaly	703	Sussman, H Absorption of undigested proteins in human beings, absorption of unaltered egg protein in adults	409
Root, H F Utilization of Jerusalem artichokes by patient with diabetes	64	Sweeny, J S Comparison of effects of general diets and of standardized diets on tolerance for dextrose	872
Rosenblatt, M S Thyroid disease, an experimental study	1	Syllaba, L Epidemic encephalitis, as observed at first Czech medical clinic in Prague	151
Rowland, R S Xanthomatosis and reticuloendothelial system, correlation of an unidentified group of cases described as defects in membranous bones, exophthalmos and diabetes insipidus (Christian's syndrome)	611	Synovial fluid, in chronic arthritis, bacteriology and cytology	675
Sakurai, E Pancreatic function, quantitative estimation of pancreatic secretion	270	Syphilis, of stomach, with special reference to diagnostic criteria	718
Scapula, of the Chinese, some observations on	508	Talbot, E P Continued administration of iodide and other salts, comparative effects on weight and growth of body	579
Scleroderma, calcinosis and	467	Tapeworm, anemia	313
Secretin, not a hemopoietic stimulant	762	Thaysen, T E H Pancreatogenous fatty diarrhea, report of case	352
Seedlings, growth, effects of serums from normal and anemic persons on	909		
Septicemia, due to strain of bacillus mucosus capsulatus group in case of diabetes mellitus	331		
Serums, from normal and anemic persons, effect of, on growth of seedlings	909		

INDEX TO VOLUME 42

	PAGE		PAGE
Thomas, W A New clinical test for tissue thirst	776	Weiss, C Bronchomoniliasis, report of case from Porto Rico	500
Thyroid disease	1	Weiss, M M Disease of coronary arteries, occurrence without gross cardiac hypertrophy	74
gland, and basal metabolism	47	Whitten M B Review of technical methods of demonstrating circulation of heart, a modification of celluloid and corrosion technic	846
hyperthyroidism, relative lymphocytosis in	419	Williamson C S Effect of administration of medicinal iron on iron reserve, an experimental study	600
relationship of parathyroid glands to, with special reference to hyperthyroidism	546	Wishnofsky, M Dextrose tolerance test, its use in determination of severity of diabetes	443
Tissue thirst, new clinical test for	776	Work, influence of, on basal metabolism, with special reference to thyroid gland	47
Tzukahara, T Pancreatic function, pancreatic activity in diabetes mellitus	560	physiologic, and arterial hypertension	297
Ulcers See Peptic Ulcer		Wright, L M Ingested creatin, its utilization and rate of excretion by arthritic and normal subjects	901
Upjohn, L B Effects of serums from normal and anemic persons on growth of seedlings	909	Xanthomatosis, and reticulo endothelial system	611
Urea, tolerance test, an index of renal function	877	Yu, H Bacteriology of rheumatic fever and allergic hypothesis	301
Uremia, experimental uremia uremic enteritis	835	Zinn, W F Ulceration of esophagus, experimental study	521
Vitamins, does commercial insulin contain what has hitherto been called vitamin B?	780	Zinzzler, H Bacteriology of rheumatic fever and the allergic hypothesis	301
Walzer, M Absorption of undigested proteins in human beings, the absorption of unaltered egg protein in adults	409	Ziskin, T Electrocardiogram in hypertension	512
Absorption of undigested proteins in human beings, absorption of unaltered fish proteins in adults	172		
Weight and growth, of body, continued administration of iodide and other salts and comparative effects on	579		

